(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 September 2001 (20.09.2001)

PCT

(10) International Publication Number
WO 01/69415 A2

(51) International Patent Classification[7]: G06F 17/00

(21) International Application Number: PCT/IB01/00468

(22) International Filing Date: 13 March 2001 (13.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/189,612 15 March 2000 (15.03.2000) US
60/216,182 6 July 2000 (06.07.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with declaration under Article 17(2)(a); without abstract; title not checked by the International Searching Authority*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/69415 A2

(54) Title: METHODS, SOFTWARE, AND APPARATI FOR DESIGNING, ORDERING, PRICING, TRACKING AND DIRECTING PRODUCTION OF CUSTOM BIOLOGICALS

(57) Abstract:

METHODS, SOFTWARE, AND APPARATI FOR DESIGNING, ORDERING, PRICING, TRACKING AND DIRECTING PRODUCTION OF CUSTOM BIOLOGICALS

Background

Field of the Invention

This invention relates to systems and methods for ordering custom designed biological molecules through networked electronic systems such as Internet. More specifically, this invention relates to electronic systems and methods for pricing, bidding, ordering, tracking and receiving custom-designed oligonucleotides.

Description of the Related Art

The advent of biotechnology has provided a vast array of reagents, engineered organisms, and biological information that has proven indispensable in pharmaceutical research and development. It is the broad range of diversity of these products and information which make them extremely useful in meeting the multifaceted needs of this industry and makes them extremely difficult to produce, price and market by any known standardized business method.

Most laboratories, at one time or another, need to order custom made biologicals in order to perform their research. These custom made biologicals include, but are not limited to, macromolecule reagents such as DNA, RNA, or protein. Custom biologicals also include modified animals, and genomic data.

One particularly useful type of custom biological reagent is an oligonucleotide. Oligonucleotides are short fragments of DNA. The use of oligonucleotides has grown significantly over the past decade as a consequence of the simultaneous burst of research and practical applications in the field of molecular biology – in particular genomic research, genetic testing and diagnostic applications– and the capacity to produce large numbers of synthetic oligonucleotides at a relatively low cost.

Oligonucleotides, along with enzymes and buffers, have become one of the most common and widely used laboratory reagents. However, oligonucleotides are different from other routine laboratory reagents in that they each have unique DNA sequences that are specific to their intended use.

In order to perform oligonucleotide-based experiments, molecular biologists carefully design the nucleotide sequences of the oligonucleotides. Modifications in the sequence of the oligonucleotides result in different products that frequently perform differently.

Besides the DNA sequence, a wide range of chemical modifications can be made to the nucleotide bases or the linkages between each base. There are additional parameters such as concentration, quantity, format and the level of purity of an oligonucleotide that can significantly

alter its performance and modify the results of an experiment. Thus, oligonucleotides are laboratory reagents that require a high degree of customization among an almost unlimited number of combinations.

Because of the complexity in designing appropriate oligonucleotide sequences, on-line ordering systems for purchasing oligonucleotides are very inflexible, and only allow the purchase of standard oligonucleotide sequences. Nor can the companies provide a price quote without having received a detailed description of the oligonucleotide.

To summarize, oligonucleotides are laboratory reagents that require a high degree of customization while being widely used on a daily basis. A sophisticated tool that facilitates the interactions between the oligonucleotide customers and the oligonucleotide vendors, as well as the interactions with the administrative systems of both parties would be a significant advantage over the systems currently available.

Summary

The instant invention provides methods, software and apparati that enables a vast array of custom biologicals and biological information to be provided to the end user facilitating the design, pricing, ordering, tracking, and directing the production of customized biologicals in a novel unified platform.

Detailed Description

Embodiments of the invention relate to electronic systems and methods for ordering custom-designed biological compounds. Although aspects of the invention involve custom-designed oligonucleotides, other custom biologicals could be similarly ordered and processed within the system. For example, custom antibodies, custom gene sequences, custom single nucleotide polymorphisms and the like can be ordered using embodiments of the present invention system.

A. Definitions

1. Biologicals

Biologicals include macromolecule reagents, modified animals, and genomic data.

2. Macromolecule Reagents

Macromolecule reagents include, but are not limited to oligonucleotides, polynucleotides, polypeptides, arrays of polynucleotides, arrays of polypeptides, both polyclonal and monoclonal antibodies, full-length and partial cDNA clones, mRNA, and genomic sequences.

3. Modified Animals

Modified animals include, but are not limited to, animals which have been treated to produce antibodies to a specified polypeptide sequence as described below in the Antibody Embodiments section, and transgenic animals (including knock-outs, knock-ins, as well as genomic substitutions).

4. Genomic Data

Genomic data includes the identity and/or frequency of SNPs and other polymorphism, cDNA sequences, genomic sequences, the positions of introns, exons, promoters, open reading frames and regions of nucleotide and amino acid sequence homology.

5. Oligonucleotides

As used interchangeably herein, the terms "oligonucleotides", "nucleic acids" and "polynucleotides" include RNA, DNA, or RNA/DNA hybrid sequences of more than one nucleotide in either single chain or duplex form.

6. Nucleotide

The term "nucleotide" as used herein as an adjective to describe molecules comprising RNA, DNA, or RNA/DNA hybrid sequences of any length in single-stranded or duplex form. The term "nucleotide" is also used herein as a noun to refer to individual nucleotides or varieties of nucleotides, meaning a molecule, or individual unit in a larger nucleic acid molecule, comprising a purine or pyrimidine, a ribose or deoxyribose sugar moiety, and a phosphate group, or phosphodiester linkage in the case of nucleotides within an oligonucleotide or polynucleotide. Although the term "nucleotide" is also used herein to encompass "modified nucleotides" which comprise at least one modifications (a) an alternative linking group, (b) an analogous form of purine, (c) an analogous form of pyrimidine, or (d) an analogous sugar, for examples of analogous linking groups, purine, pyrimidines, and sugars see for example PCT publication No. WO 95/04064. The desired polynucleotide sequences are preferably chemically synthesized, but may also be prepared by any known method, including semi-synthetic, recombinant, *ex vivo* generation, or a combination thereof, as well as utilizing any purification methods known in the art.

Throughout the present specification, the expression "nucleotide sequence" may be employed to designate indifferently a polynucleotide or a nucleic acid. More precisely, the expression "nucleotide sequence" encompasses the nucleic material itself and is thus not restricted to the sequence information (i.e. the succession of letters chosen among the four base letters) that biochemically characterizes a specific DNA or RNA molecule.

7. **Polypeptide**

The term "polypeptide" refers to a polymer of amino without regard to the length of the polymer; thus, peptides, oligopeptides, and proteins are included within the definition of polypeptide. This term also does not specify or exclude post-expression modifications of polypeptides, for example, polypeptides which include the covalent attachment of glycosyl groups, acetyl groups, phosphate groups, lipid groups and the like are expressly encompassed by the term polypeptide. Also included within the definition are polypeptides which contain one or more analogs of an amino acid (including, for example, non-naturally occurring amino acids, amino acids which only occur naturally in an unrelated biological system, modified amino acids from mammalian systems etc.), polypeptides with substituted linkages, as well as other modifications known in the art, both naturally occurring and non-naturally occurring.

8. **Recombinant Polypeptide**

The term "recombinant polypeptide" is used herein to refer to polypeptides that have been artificially designed and which comprise at least two polypeptide sequences that are not found as contiguous polypeptide sequences in their initial natural environment, or to refer to polypeptides which have been expressed from a recombinant polynucleotide.

9. **Expression Vector**

The expression vector is any of the mammalian, yeast, insect or bacterial expression systems known in the art. Commercially available vectors and expression systems are available from a variety of suppliers including Genetics Institute (Cambridge, MA), Stratagene (La Jolla, California), Promega (Madison, Wisconsin), and Invitrogen (San Diego, California). If desired, to enhance expression and facilitate proper protein folding, the codon context and codon pairing of the sequence is optimized for the particular expression organism in which the expression vector is introduced, as explained by Hatfield, et al., U.S. Patent No. 5,082,767.

10. **Antibody**

As used herein, the term "antibody" refers to a polypeptide or group of polypeptides which are comprised of at least one binding domain, where an antibody binding domain is formed from the folding of variable domains of an antibody molecule to form three-dimensional binding spaces with an internal surface shape and charge distribution complementary to the features of an antigenic determinant of an antigen, which allows an immunological reaction with the antigen. Antibodies include recombinant proteins comprising the binding domains, as wells as fragments, including Fab, Fab', $F(ab)_2$, and $F(ab')_2$ fragments.

11. Antigenic Determinant

As used herein, an "antigenic determinant" is the portion of an antigen molecule, in this case a desired polypeptide, that determines the specificity of the antigen-antibody reaction. An "epitope" refers to an antigenic determinant of a polypeptide. An epitope can comprise as few as 3 amino acids in a spatial conformation which, is unique to the epitope. Generally an epitope consists of at least 6 such amino acids, and more usually at least 8-10 such amino acids. Methods for determining the amino acids which make up an epitope include x-ray crystallography, 2-dimensional nuclear magnetic resonance, and epitope mapping e.g. the Pepscan method described by H. Mario Geysen et al. 1984. Proc. Natl. Acad. Sci. U.S.A. 81:3998-4002; PCT Publication No. WO 84/03564; and PCT Publication No. WO 84/03506.

12. Transgenic Animals

The terms "transgenic animals" or "host animals" used herein designate animals that have their genome genetically and artificially manipulated. Preferred animals are non-human mammals and include those belonging to a genus selected from *Mus* (e.g. mice), *Rattus* (e.g. rats) and *Oryctogalus* (e.g. rabbits) which have their genome artificially and genetically altered by the insertion of a nucleic acid according to the invention. The desired transgenic animals all include within a plurality of their cells a cloned recombinant or synthetic DNA sequence. Preferred transgenic animals according to the invention contain in their somatic cells and/or in their germ line cells a specified polynucleotide. The desired transgenic animals thus contain specific sequences of exogenous genetic material which are specified by the genomic sequence to be added, removed or modified in a suitably configured player module. The design of the desired transgenic animals may be made according to the conventional techniques well known for one skilled in the art. For more details regarding the production of transgenic animals, and specifically transgenic mice, one may refer to US Patents Nos. 4,873,191, issued Oct.10, 1989, 5,464,764 issued Nov. 7, 1995 and 5,789,215, issued Aug. 4, 1998.

13. Database

A database includes indexed and freeform tables for storing data. Within each table are a series of fields that store data strings, such as names, addresses, chemical names, and the like. However, it should be realized that several types of databases are available. For example, a database might only include a list of data strings arranged in a column. Other databases might be relational databases wherein several two dimensional tables are linked through common fields. Embodiments of the invention are not limited to any particular type of database.

14. Input Devices

An input device can be, for example, a keyboard, rollerball, mouse, voice recognition system, automated script from another computer that generates a file, or other device capable of transmitting information from a customer to a computer. The input device can also be a touch screen associated with the display, in which case the customer responds to prompts on the display by touching the screen. The customer may enter textual information through the input device such as the keyboard or the touch-screen.

15. Instructions

Instructions refer to computer-implemented steps for processing information in the system. Instructions can be implemented in software, firmware or hardware and include any type of programmed step undertaken by components and modules of the system.

16. LAN

One example of a Local Area Network may be a corporate computing network, including access to the Internet, to which computers and computing devices comprising the system are connected. In one embodiment, the LAN conforms to the Transmission Control Protocol/Internet Protocol (TCP/IP) industry standard. In alternative embodiments, the LAN may conform to other network standards, including, but not limited to, the International Standards Organization's Open Systems Interconnection, IBM's SNA, Novell's Netware, and Banyan VINES.

17. Microprocessor

A microprocessor as used herein may be any conventional general purpose single- or multi-chip microprocessor such as a Pentium® processor, a Pentium® Pro processor, a 8051 processor, a MIPS® processor, a Power PC® processor, or an ALPHA® processor. In addition, the microprocessor may be any conventional special purpose microprocessor such as a digital signal processor or a graphics processor. The microprocessor typically has conventional address lines, conventional data lines, and one or more conventional control lines.

18. Modules

The system is comprised of various modules as discussed in detail below. As can be appreciated by one of ordinary skill in the art, each of the modules comprises various sub-routines, instructions, commands, procedures, definitional statements and macros. Each of the modules are typically separately compiled and linked into a single executable program. Therefore, the following description of each of the modules is used for convenience to describe the functionality of the preferred system. Thus, the processes that are undergone by each of the modules may be arbitrarily

redistributed to one of the other modules, combined together in a single module, or made available in, for example, a shareable dynamic link library.

19. Networks

The system may include any type of electronically connected group of computers including, for instance, the following networks: Internet, Intranet, Local Area Networks (LAN) or Wide Area Networks (WAN). In addition, the connectivity to the network may be, for example, remote modem, Ethernet (IEEE 802.3), Token Ring (IEEE 802.5), Fiber Distributed Datalink Interface (FDDI) or Asynchronous Transfer Mode (ATM). Note that computing devices may be desktop, server, portable, hand-held, set-top, or any other desired type of configuration. As used herein, an Internet includes network variations such as public internet, a private internet, a secure internet, a private network, a public network, a value-added network, an intranet, and the like.

20. Operating Systems

The system may be used in connection with various operating systems such as: UNIX, Disk Operating System (DOS), OS/2, Windows 3.X, Windows 95, Windows 98, Windows 2000 and Windows NT.

21. Player

As used herein, the term "player" refers to a compiled user interface program that displays information to a customer. For example a customer player is used to enter and view information relating to the custom biological that is being bid upon, ordered or tracked within the system. Preferably, the player reads data from a standard format, such as XML, and displays the corresponding data to the customer. In one embodiment, the player is based on an Internet browser that reads XML documents.

22. Programming Languages

The various software aspects of the system may be written in any programming language such as C, C++, BASIC, Pascal, Perl, Java, and FORTRAN and ran under the well-known operating system. C, C++, BASIC, Pascal, Java, and FORTRAN are industry standard programming languages for which many commercial compilers can be used to create executable code.

23. SGML

The Standard Generalized Markup Language (SGML) is an international standard for describing the structure and content of machine-readable information. SGML "documents" usually consist of text, graphics, and hypertext links. SGML identifies and names the parts of the

information so that these parts can be managed and manipulated to create a variety of products as diverse as typesetting, indexing, CD-ROM distribution, serving as hypertext over the Web, and translation into foreign languages. Information on the specification for SGML can be found on the Internet at http://www.w3.org.

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24. Standard Data Format

A standard data format includes a pre-determined definition of how data is to be sent from one system/module to another. By defining a standard data format for custom biologicals orders, the system can send the same data file to several vendors in order to obtain a bid. The standard data
10 format can be based on the Extended Markup Language (XML), a Document Type Definition (DTD) or the Standard Generalized Markup Language (SGML) or other predefined format.

25. System

A system is one or more computers and associated peripherals that carry out selected
15 functions. For example, a Customer system includes the computer hardware, software and firmware for executing the specific software instructions described below. A system should not be interpreted as being limited to be a single computer or microprocessor, and may include a network of computers, or a computer having mutiple microprocessors.

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26. Transmission Control Protocol

Transmission Control Protocol (TCP) is a transport layer protocol used to provide a reliable, connection-oriented, transport layer link among computer systems. The network layer provides services to the transport layer. Using a two-way handshaking scheme, TCP provides the
25 mechanism for establishing, maintaining, and terminating logical connections among computer systems. TCP transport layer uses IP as its network layer protocol. Additionally, TCP provides protocol ports to distinguish multiple programs executing on a single device by including the destination and source port number with each message. TCP performs functions such as transmission of byte streams, data flow definitions, data acknowledgments, lost or corrupt data re-
30 transmissions and multiplexing multiple connections through a single network connection. Finally, TCP is responsible for encapsulating information into a datagram structure.

27. **XML**

The Extended Markup Language (XML) is a derivative dialect of SGML designed for use
35 on the World Wide Web and in intranets. XML is a stripped-down version of SGML. Thus, every valid XML document is also a valid SGML document. XML is therefore useful for implementing

the most commonly-used SGML features. The specification for XML can be found on the Internet at http://www.w3.org.

B. Overview of the System

By using embodiments of the system described below, a customer can efficiently determine, bid and order a variety of custom biologicals. Once the biological is determined, the customer enters a description of the molecule into a bidding module. The bidding module then sends the description, in a standard data format such as the Extended Markup Language (XML), to a transaction server.

The transaction server analyzes the type of order and determines the appropriate vendors capable of developing the custom biological. Thus, if the biological is a custom antibody, only vendors with the capability to provide antibodies will be contacted. Once the list of appropriate vendors has been determined, the system sends a standard data format bid request to each vendor.

Once each vendor receives the order, their system automatically or manually determines a bid for completing the required task. In one embodiment, the task could be producing a custom antibody that binds to a selected peptide sequence. In this embodiment, the order could include the amino acid sequence of the polypeptide, the required quantity of antibody, and other specific information necessary for each vendor to provide its bid. Once the bid is determined from each vendor, the vendor system returns a standard data format document to the transaction server that reports the bid price and any other useful information, such as purity, manufacturing time estimates and the like.

The transaction server orders the returned bid data by, for example, price or manufacturing times and then forwards that information to the customer that placed the order. The customer can then review the bids and select the most desirable bid from among those that have been returned.

In one preferred embodiment, the system is used to order custom designed oligonucleotide sequences. In this embodiment, the custom biological is the nucleotide sequence of the oligonucleotide. The nucleotide sequence is first entered manually or automatically into a customer module on the customer's computer. The customer module can be a stand alone program or a browser based application. In addition, the customer module can include software instructions for determining the actual sequence of the oligonucleotide to order.

For example, in one embodiment, the customer module includes a primer determination program that designs oligonucleotide primer sequences that have homology to a known sequence. There are many instances where researchers might want to order an oligonucleotide primer that binds to a particular sequence. This primer determination software would assist the researcher in determining the appropriate primer sequence to order. Well known conventional primer

determination programs are commercially available and can be incorporated within the system of the present invention by one of ordinary skill in the art.

In addition to standard nucleotide information, other information relating to the custom oligonucleotide can also be entered. This information can be, for example, the types of bonds between each chemical group (nucleotide), or other side groups that are part of the composition to be ordered. Once the information is gathered by the customer module, it is converted into a standard data format. In one embodiment, the standard data format is the Extended Markup Language (XML), but other types of standard data formats, such as the Hypertext Markup Language (HTML), SGML or other DTD could be substituted. The standard data format includes all of the information on the custom biological, plus other information, such as a unique identifier of the customer.

Once the information has been converted into a standard data format, it is transmitted to the transaction server that connects a plurality of customers to a plurality of vendors.

Within embodiments of the transaction server are two interfaces that connect the customer to the transaction server. The first interface accepts data formats from the customer relating to pricing bids for a custom designed biological. The second interface accepts data formats from the customer relating to actual orders placed for the custom biologicals. Of course, although the described embodiment provides a single transaction server, more than one transaction server could be integrated into the overall system by one of ordinary skill in the art.

Once these bids or orders have been placed by the customer, they are transmitted through the interfaces described above to each vendor. The vendors that have been sent a bid request return a price quote to the transaction server. Vendors that receive orders thereafter process the orders and send the custom biological to the customer.

It should be realized that embodiments of this invention are extensible to delivery of genomic data in addition to actual chemical compounds. For example, a customer could request a bid for providing every single nucleotide polymorphism (SNP) within particular nucleotide sequence. In this embodiment, the customer could send a nucleotide sequence to a plurality of vendors. Each vendor would then match the customer's nucleotide sequence against their database of SNPs to determine if the had any data on the requested sequence. If such SNPs were found in their database, the vendor could return a price for revealing the SNPs of the customer's nucleotide sequence. In addition, the vendor could also return a price for performing additional experiments to discover additional SNPs of the customer's nucleotide sequence.

In another embodiment, embodiments of the invention relate to returning allelic variations of a particular sequence. Similar to the method described above for SNPs, the vendor can receive bids for providing a customer with allelic variations of a particular nucleotide sequence. The vendor would then look into its own database of genetic data to determine if such variants had

already been determined. If so, the price for revealing the nucleotide sequences of such variants would be returned to the customer. Also, the vendor can provide a bid price for using the customer's nucleotide sequence to discover additional allelic variants in particular populations of individuals. If the customer accepts such a bid, the vendor then carries out the required experiments and returns the allelic gene data to the customer.

1. **Entering Custom Biologicals into The System**

Embodiments of the invention include several methods for entering custom biological data. For example, an stand-alone software "player" module can be run on the customer's computer that provides inputs for various types of custom biologicals. In one embodiment, the player is designed to accept input relating to oligonucleotides, polynucleotides, arrays of polynucleotides, full-length and partial cDNA clones, mRNA, or genomic sequences.

In this embodiment, the entire nucleotide sequence(s) to be bid or ordered can be entered into the player module. In addition, entire sequences, as well as portions of a gene, or an Expressed Sequence Tag (EST) can be entered into the player module in order to obtain extended or full-length mRNA, cDNA, genomic sequences from a vendor. In addition, the customer can enter nucleotide sequences so as to obtain information regarding the identity and/or frequency of polymorphisms, SNPs, splice variant or genetic homologues.

Similarly, the entire identity or only a portion of a polypeptide or array of polypeptides can be entered into the player module to obtain polypeptides, arrays of polypeptides, antibodies, or animals which have been treated to produce antibodies to a specified polypeptide sequence. In a preferred embodiment, vendors who own proprietary libraries or collections of custom biologicals are able to modify the pricing module to differentiate between biologicals which are already in the library and therefore cheaper to provide to the end user and those which must be custom synthesized. Embodiments which are able to deliver combinations of already existing biologicals and custom synthesized biologicals are explicitly contemplated.

Any of the desired polynucleotides can be labeled, if desired, by incorporating a label detectable by spectroscopic, photochemical, biochemical, immunochemical, or chemical means. For example, useful labels include radioactive substances, fluorescent dyes or biotin. Preferably, polynucleotides are labeled at their 3' and 5' ends. A label can also be used to capture the primer, so as to facilitate the immobilization of either the primer or a primer extension product, such as amplified DNA, on a solid support. A capture label is attached to the primers or probes and can be a specific binding member which forms a binding pair with the solid's phase reagent's specific binding member (e.g. biotin and streptavidin). Therefore depending upon the type of label carried by a polynucleotide or a probe, it may be employed to capture or to detect the target DNA.

Further, it will be understood that the polynucleotides, primers or probes provided herein, may, themselves, serve as the capture label. For example, in the case where a solid phase reagent's binding member is a nucleic acid sequence, it may be selected such that it binds a complementary portion of a primer or probe to thereby immobilize the primer or probe to the solid phase. In cases where a polynucleotide probe itself serves as the binding member, those skilled in the art will recognize that the probe will contain a sequence or "tail" that is not complementary to the target. In the case where a polynucleotide primer itself serves as the capture label, at least a portion of the primer will be free to hybridize with a nucleic acid on a solid phase. DNA Labeling techniques are well known to the skilled technician.

Any of the desired polynucleotides, primers and probes can be conveniently ordered as immobilized on a solid support. Solid supports are known to those skilled in the art and include the walls of wells of a reaction tray, test tubes, polystyrene beads, magnetic beads, nitrocellulose strips, membranes, microparticles such as latex particles, sheep (or other animal) red blood cells, duracytes® and others. The solid support is not critical and can be selected by one skilled in the art. Thus, latex particles, microparticles, magnetic or non-magnetic beads, membranes, plastic tubes, walls of microtiter wells, glass or silicon chips, sheep (or other suitable animal's) red blood cells and duracytes are all suitable examples.

Suitable methods for immobilizing nucleic acids on solid phases include ionic, hydrophobic, covalent interactions and the like. A solid support, as used herein, refers to any material which is insoluble, or can be made insoluble by a subsequent reaction. The solid support can be chosen for its intrinsic ability to attract and immobilize the capture reagent. Alternatively, the solid phase can retain an additional receptor which has the ability to attract and immobilize the capture reagent. The additional receptor can include a charged substance that is oppositely charged with respect to the capture reagent itself or to a charged substance conjugated to the capture reagent. As yet another alternative, the receptor molecule can be any specific binding member which is immobilized upon (attached to) the solid support and which has the ability to immobilize the capture reagent through a specific binding reaction. The receptor molecule enables the indirect binding of the capture reagent to a solid support material before the performance of the assay or during the

ordered array of polynucleotides is designed to be "addressable" where the distinct locations are recorded and can be accessed as part of an assay procedure.

Addressable polynucleotide arrays typically comprise a plurality of different oligonucleotide probes that are coupled to a surface of a substrate in different known locations. The knowledge of the precise location of each polynucleotides location makes these "addressable" arrays particularly useful in hybridization assays. Any addressable array technology known in the art can be employed with the desired polynucleotides. One particular embodiment of these polynucleotide arrays is known as the Genechips™, and has been generally described in US Patent 5,143,854; PCT publications WO 90/15070 and 92/10092. These arrays may generally be produced using mechanical synthesis methods or light directed synthesis methods, which incorporate a combination of photolithographic methods and solid phase oligonucleotide synthesis (Fodor et al., *Science*, 251:767-777, 1991). The immobilization of arrays of oligonucleotides on solid supports has been rendered possible by the development of a technology generally identified as "Very Large Scale Immobilized Polymer Synthesis" (VLSIPS™) in which, typically, probes are immobilized in a high density array on a solid surface of a chip. Examples of VLSIPS™ technologies are provided in US Patents 5,143,854 and 5,412,087 and in PCT Publications WO 90/15070, WO 92/10092 and WO 95/11995, which describe methods for forming oligonucleotide arrays through techniques such as light-directed synthesis techniques. In designing strategies aimed at providing arrays of nucleotides immobilized on solid supports, further presentation strategies were developed to order and display the oligonucleotide arrays on the chips in an attempt to maximize hybridization patterns and sequence information. Examples of such presentation strategies are disclosed in PCT Publications WO 94/12305, WO 94/11530, WO 97/29212 and WO 97/31256.

Oligonucleotides comprising modified nucleotides are also included in the present invention. Oligonucleotides may, for example, contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. Modifications of the present invention include, but are not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid

(v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

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2. **Price Quotes**

Once a customer has placed an order, the first interface in a transaction server receives the bit request in a standard data format. The bid request includes bulk listing of the structure and features of the custom biological in order to calculate prices. Thus, in this embodiment, the exact 10 composition of the custom biological does not have to be transmitted across the Internet. For example, if the composition is an oligonucleotide, information relating to the total number of nucleotides, identity and number of custom bonds and the total quantity of DNA required might be sufficient to prepare a bid. The actual sequence of the oligonucleotide would not need to be sent to the transaction server.

15 Of course, it should be realized that conventional encrypton techniques can be employed to encrypt the transmission between the customer and the transaction server. For example, digital certificates, such as those available from Verisign Corporation (www.verisign.com) could be used by the customer and transaction server to encrypt messages and authenticate customers.

Once the bid request is received by the transaction server, it is transmitted to a plurality of 20 vendors in order to obtain price quotes. The transaction server sends the standard data format to each vendor and tracks which vendor has been sent a quote request. Once a price quote has been received from each vendor, the transaction server forwards the price quotes to the requesting customer. As can be envisioned, this system thus provides an exchange or "reverse auction" that can be used by custom chemical composition buyers to determine the best price for synthesizing the 25 requested product. As discussed above, the communication between the vendors and the transaction server is preferably encrypted and digitally signed to ensure that the data has not been tampered with or altered.

Because the transaction server sends its information in a standard data format, albeit preferably encrypted, such as XML, each vendor can provide their own custom interface that reads 30 this standard format and imports the necessary data into the vendor's quoting system. Thus, many different vendors, running many different operating systems and software can participate in the system. In addition, because each vendor will output a price quote in a standard data format, the transaction server reads the standardized incoming data and provides a pricing comparison for the customer.

35 It should also be understood that each vendor can be an "exchange vendor" that controls access to a subset of other vendors. Thus, each exchange vendor would receive the bid request and

transmit it to its subset of vendor that would actually bid on providing the custom biological compound. Examples of these types of exchange vendors include Chemdex (www.chemdex.com) and SciQuest (www.sciquest.com).

In one embodiment, in order for the vendors to properly quote prices for the custom compositions, the vendor system includes a bid module that received the bid requests based upon the standard data format. The bid module provides three databases: 1) a customer name database, 2) a contract price database and 3) a standard price database.

The customer name database preferably contains the names, preferences and unique customer identifiers for each customer that is authorized to request price quotes and orders in the system. The preferences can be for default parameters such as the normal delivery time requested, standard quantities ordered and preferred sample format (liquid, powder, etc.).

The contract price database includes fields that store contract provisions for each customer so that specific customers can be provided with special prices. For example, a particularly good customer might be provided with a ten percent discount over the standard price. Other fields in the database store contract provisions for penalties or dollar value purchase limits.

The standard price database includes fields corresponding to standard prices for each of the options available to the customers. Thus, if a contractual price for the customer is not found, the system will produce a price quote by reference to the standard price database. For example, the standard prices of each nucleotide sequence might be $1.00.

3. Placing Orders

The second interface in the transaction server receives the custom biological orders from a customer. These orders are sent in a standard data format that provides all of the necessary order information to a vendor. It should be realized that although this process has been described as providing a price bid before an order is placed, an order could be placed by a customer without ever requesting a price bid with a vendor. This might be appropriate, for example, when a customer desires to purchase their custom chemical composition from a particular vendor.

Once the second interface has received an order from a customer, the order is logged into an order tracking module within the transaction server so that the status of the order with the vendor can be tracked. The order is then sent in a standard data format to the predetermined vendor. The vendor computer then processes the order and sends a confirmation of order receipt to the transaction server. The transaction server logs the confirmation, and forwards the confirmation to the customer.

Once the order has been entered into an order database in the vendor system, it also placed within a vendor tracking module. This module is used by the vendor to track the status of orders within the vendor system. The order is then transferred to a production module that is responsible

for overseeing the actual production processing of the order. For example, if the order was for an oligonucleotide, the production module would send the desired nucleotide sequence to a data conversion module so that it is put in the proper data format for an oligonucleotide synthesizer. The converted data is then forwarded to the synthesizer so it can be manufactured. Because the process may not require human intervention, the chance of synthesis errors is greatly diminished.

Once the order is placed, the transaction server monitors the status of the order and reports back to the customer via data transmission to the player. After the desired product has been synthesized and ready for shipment, an accounting system within the vendor system prepares the appropriate invoice and billing options according to the terms of the purchase order that was sent with the order.

The product is then shipped from the vendor to the customer, and the customer is automatically billed by the vendor for the service. It should also be realized that the transaction server can be integrated into the accounting process so that a dollar amount from each order that is completed by a vendor is sent to the host (i.e. Genset, Sciquest, Chemdex or other exchange) of the transaction server. Thus, the host of the transaction server can be provided with a revenue stream for providing the bidding and ordering process to the customers and vendors. In addition, the system can be provided so that the actual bill for the custom designed product is sent from the host of the transaction server to the customer. The host of the transaction server then pays the vendor directly. In this manner, the host of the transaction server can charge one fee to the customer, and pay a lower fee to the vendor for manufacturing the product.

It should also be realized that a bid is not required prior to placing an order. A customer can simply place an order for a chemical compound through the order module and designate a particular vendor. The transaction server will pass the order directly to the particular vendor and begin the process of ordering the custom biological.

4. Manufacturing Biologicals

a. Oligonucleotides

The desired oligonucleotides are preferably synthesized chemically as directed by a standardized data file fed into the production module and utilizing various chemical methods well known in the art, e.g. by use of an automated DNA synthesizer (such as a 380B automatic DNA synthesizer (Applied Biosystems, Foster City, Calif.). As examples, the methods of Caruthers, M. H. et al. (1980) Nucl. Acids Res. Symp. Ser. 215-223, and Horn, T. et al. (1980) Nucl. Acids Res. Symp. Ser. 225-232. may be used to synthesize oligonucleotides. Phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. (Nucl. Acids Res. 16:3209, 1988), and methylphosphonate oligonucleotides may be prepared by use of controlled pore glass polymer supports (Sarin et al., Proc. Natl. Acad. Sci. USA 85:7448, 1988).

b. Polypeptides

The desired polypeptides are preferably synthesized chemically as directed by a standardized data file fed into the production module and utilizing various chemical methods well known in the art including solid phase techniques such as those described in: Fields et al, Int. J. Peptide Protein Res., 35: 161-214 (1990); Roberge, J. Y. et al. (1995) Science 269:202-204); and Merrifield, J. Am. Chem. Soc., 85: 2149 (1964); Houghten, Proc. Natl. Acad. Sci. USA, 82: 5132 (1985). Polypeptides may also be produced by automated synthesis using the ABI 431 A Peptide Synthesizer (Perkin Elmer), for example.

The newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (e.g., Creighton, T. (1983) Proteins, Structures and Molecular Principles, WH Freeman and Co., New York, N.Y.). The composition of the synthetic peptides may be confirmed by amino acid analysis or sequencing (e.g., the Edman degradation procedure; Creighton, supra). Additionally, the amino acid sequence of the polypeptides, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

The desired polypeptides may be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 amino acids naturally occurring in humans as specified in the standardized data file entered into the production module. The polypeptides may be modified by either natural processes, such as post-translational processing, or by chemical modification techniques which are well known in the art. Specific modifications may be made anywhere in the polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. The same type of modification may be made in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. The polypeptides may be branched , for example, as a result of ubiquitination, and they may be cyclic, with or without branching.

Cyclic, branched, and branched cyclic polypeptides may result from post-translation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA

mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992).

The desired polypeptides can also be made using routine expression methods known in the art. The polynucleotide encoding the desired polypeptide is ligated into an expression vector suitable for any convenient host. Both eukaryotic and prokaryotic host systems are used in forming recombinant polypeptides. The polypeptide is then isolated from lysed cells or from the culture medium and purified to the extent needed for its intended use. Purification is by any technique known in the art, for example, differential extraction, salt fractionation, chromatography, centrifugation, and the like. See, for example, Methods in Enzymology for a variety of methods for purifying proteins.

Methods for purifying proteins are known in the art, and include the use of detergents or chaotropic agents to disrupt particles followed by differential extraction and separation of the polypeptides by ion exchange chromatography, affinity chromatography, sedimentation according to density, and gel electrophoresis.

Standard methods are published in methods texts such as Davis et al., (Basic Methods in Molecular Biology, L.G. Davis, M.D. Dibner, and J.F. Battey, ed., Elsevier Press, NY, 1986) and many of the methods are available from Stratagene, Life Technologies, Inc., or Promega. Polypeptide may additionally be produced from the construct using in vitro translation systems such as the In vitro Express™ Translation Kit (Stratagene).

c. Antibodies

Non-human animals or mammals, whether wild-type or transgenic, which express a different species of the desired protein than the one to which antibody binding is desired, and animals which do not express desired protein (i.e. an knock out animal as described in herein) are useful for preparing antibodies. The transgenic mice for example those developed by Abgenix or Medarex which are able to produce partially or totally humanized antibodies are also particularly useful for generating antibodies to be used as therapeutics and in vivo diagnostic reagents. Phage display technologies, for example those developed by Dyax or Morphosys, are particularly useful in generating antibodies for use as low cost research tools.

Substantially pure protein or polypeptide is chemically synthesized as described above in the Polypeptide Embodiments section, or isolated from transfected or transformed cells containing an expression vector encoding the desired protein or a portion thereof. The polypeptide antigens are

preferably synthesized chemically as directed by a standardized data file fed into the production module and utilizing various chemical methods well known in the art. The concentration of protein in the final preparation is adjusted, for example, by concentration on an Amicon filter device, to the level of a few micrograms per ml. Monoclonal or polyclonal antibodies to the protein can then be prepared as follows:

Monoclonal antibody to epitopes in the desired protein or a portion thereof can be prepared from murine hybridomas according to the classical method of Kohler and Milstein (Nature, 256:495, 1975) or derivative methods thereof (see Harlow and Lane, Antibodies A Laboratory Manual, Cold Spring Harbor Laboratory, pp. 53-242, 1988).

Briefly, a mouse is repetitively inoculated with a few micrograms of the desired protein or a portion thereof over a period of a few weeks. The mouse is then sacrificed, and the antibody producing cells of the spleen isolated. The spleen cells are fused by means of polyethylene glycol with mouse myeloma cells, and the excess unfused cells destroyed by growth of the system on selective media comprising aminopterin (HAT media). The successfully fused cells are diluted and aliquots of the dilution placed in wells of a microtiter plate where growth of the culture is continued. Antibody-producing clones are identified by detection of antibody in the supernatant fluid of the wells by immunoassay procedures, such as ELISA, as originally described by Engvall, E., Meth. Enzymol. 70:419 (1980). Selected positive clones can be expanded and their monoclonal antibody product harvested for use. Detailed procedures for monoclonal antibody production are described in Davis, L. et al. Basic Methods in Molecular Biology Elsevier, New York. Section 21-2.

Polyclonal antiserum containing antibodies to heterogeneous epitopes in the desired protein or a portion thereof can be prepared by immunizing suitable non-human animal with the desired protein or a portion thereof, which can be unmodified or modified to enhance immunogenicity. A suitable non-human animal is preferably a non-human mammal is selected, usually a mouse, rat, rabbit, goat, or horse. Alternatively, a crude preparation which, has been enriched for the desired protein concentration can be used to generate antibodies. Such proteins, fragments or preparations are introduced into the non-human mammal in the presence of an appropriate adjuvant (e.g. aluminum hydroxide, RIBI, etc.) which is known in the art. In addition the protein, fragment or preparation can be pretreated with an agent which will increase antigenicity, such agents are known in the art and include, for example, methylated bovine serum albumin (mBSA), bovine serum albumin (BSA), Hepatitis B surface antigen, and keyhole limpet hemocyanin (KLH). Serum from the immunized animal is collected, treated and tested according to known procedures. If the serum contains polyclonal antibodies to undesired epitopes, the polyclonal antibodies can be purified by immunoaffinity chromatography.

Effective polyclonal antibody production is affected by many factors related both to the antigen and the host species. Also, host animals vary in response to site of inoculations and dose,

with both inadequate or excessive doses of antigen resulting in low titer antisera. Small doses (ng level) of antigen administered at multiple intradermal sites appears to be most reliable. Techniques for producing and processing polyclonal antisera are known in the art, see for example, Mayer and Walker (1987). An effective immunization protocol for rabbits can be found in Vaitukaitis, J. et al. J. Clin. Endocrinol. Metab. 33:988-991 (1971). Booster injections can be given at regular intervals, and antiserum harvested when antibody titer thereof, as determined semi-quantitatively, for example, by double immunodiffusion in agar against known concentrations of the antigen, begins to fall. See, for example, Ouchterlony, O. et al., Chap. 19 in: Handbook of Experimental Immunology D. Wier (ed) Blackwell (1973). Plateau concentration of antibody is usually in the range of 0.1 to 0.2 mg/ml of serum (about 12 :M). Affinity of the antisera for the antigen is determined by preparing competitive binding curves, as described, for example, by Fisher, D., Chap. 42 in: Manual of Clinical Immunology, 2d Ed. (Rose and Friedman, Eds.) Amer. Soc. For Microbiol., Washington, D.C. (1980).

Antibody preparations prepared according to either the monoclonal or the polyclonal protocol are useful in quantitative immunoassays which determine concentrations of antigen-bearing substances in biological samples; they are also used semi-quantitatively or qualitatively to identify the presence of antigen in a biological sample. The antibodies may also be used in therapeutic compositions for killing cells expressing the protein or reducing the levels of the protein in the body.

d. Transgenic Animals

Desired transgenic animals are produced by the application of procedures which result in an animal with a genome that has incorporated exogenous genetic material. A recombinant polynucleotide is inserted into an embryonic or ES stem cell line. The insertion is preferably made using electroporation, such as described by Thomas et al. (*Cell* 51:503-512, 1987). The cells subjected to electroporation are screened (e.g. by selection via selectable markers, by PCR or by Southern blot analysis) to find positive cells which have integrated the exogenous recombinant polynucleotide into their genome, preferably via an homologous recombination event. An illustrative positive-negative selection procedure that may be used according to the method is described by Mansour et al. (*Nature* 336:348-352, 1988).

Then, the positive cells are generally isolated, cloned and injected into 3.5 days old blastocysts from mice, such as described by Bradley ("Production and Analysis of Chimaeric Mice," *E.J. Robertson (Ed.), Teratocarcinomas and embryonic stem cells: A practical approach* IRL Press, Oxford, 113, 1987). The blastocysts are then inserted into a female host animal and allowed to grow to term.

Alternatively, the positive ES cells are brought into contact with embryos at the 2.5 days old 8-16 cell stage (morulae) such as described by Wood et al. (*Proc. Natl. Acad. Sci. U.S.A.* 90:4582-4585, 1993) or by Nagy et al. (*Proc. Natl. Acad. Sci. USA*. 90: 8424-8428, 1993), the ES cells being

internalized to colonize extensively the blastocyst including the cells which will give rise to the germ line. The offspring of the female host are tested to determine which animals are transgenic e.g. include the inserted exogenous DNA sequence and which are wild-type.

5. Oligonucleotide Ordering Embodiment

Embodiments of the system include a series of executable software programs that interact with each other through communication protocols over a network utilizing standard data formats. Features of the system include:

- The design and editing of a bid request and/or order comprising the oligonucleotide sequence, characteristics and specifications by the customer.
- A bid request for processing the designed oligonucleotide to be ordered as well as a picklist of vendors allowed to bid on the request.
- Processing of a request for Purchase Order numbers and approval from its Administration by the customer.
- Sending of the order to the Vendor by the customer.
- Tracking of the order by the customer during its processing by the Vendor and/or Manufacturer.
- Invoicing by the Vendor to the Administration.
- Payment by the Administration to the Vendor.

Referring to Figure 1, one embodiment of a custom oligonucleotide bid and order system 10 is illustrated. As shown, the system 10 includes several systems and modules. A set of customer systems 15A,B are linked to administration systems 20A,B. Within each customer system is a bid module 25A,B and an order module 27A,B. Additionally, the customer systems 15A,B can include sequence analysis modules 28A,B that provide programs for creating, ordering and analyzing nucleotide or peptide sequences. Such sequence analysis modules are discussed previously in relation to determining custom primers that bind to a particular nucleotide sequence. The customer systems are linked through a network, such as the Internet, to a transaction server 30 which processes data transactions from the customer computers.

The transaction server 30 is linked to three vendor systems 35A-C which provide the custom biologicals that are ordered by each customer. Within each vendor system is a vendor order module 37A-C for processing actual orders and a vendor bid module 40A-C for processing price quotes to customers. In addition, a synthesizer 45A-C is linked to each of the vendor systems. The synthesizer 45 can produce nucleotide sequences, or in another embodiment, synthesize peptide sequences.

a. Customer System

As illustrated in Figure 2, the customer system 15 includes several modules for carrying out the tasks described below. These modules are preferably compiled into a single executable "player"

that is installed on the customer's computer, however one of ordinary skill could separate these modules into two or more stand-alone executable programs.

Preferably, the customer system is a standard computer system such as that based on an Intel Pentium processor and running a Microsoft Windows operating system, such as Windows 98, Windows 2000 or Windows NT. The customer system 15 can be run in a stand alone, disconnected mode to perform local functions including without limitation: the preparation of new orders, and the management of archived orders and all related data. It should be understood that when in this mode, the player can "burst" data to the transaction server 30 when the customer system 15 becomes linked to the transaction server. In one embodiment, a data queue is provided within the player that stores and tracks which messages need to be sent to the transaction server once a connection is detected.

The customer system 15 can also be run in an interactive, connected mode to perform on-line, real-time communication tasks with the Administration system 20 and the vendor system 35, through the transaction server. This communication includes, without limitation, the transmission of bid requests to the vendor system, the transmission of purchase order approval requests and purchase order number requests to the administration system, the transmission of orders to the vendor system, the receipt of quotes from the vendor system and the reception of tracking order information from the vendor system.

As shown in Figure 2, the customer system 15 includes a customer profiles database that stores data relating to the customer that is entering data into the system. The customer profile database verifies access privileges with the assistance of an authentication module 110 and provides customer information, such as name and identification numbers to the other modules of the customer system. The authentication module 110 provides secured access to the ordering process by requiring a password from the customer. This prevents unauthorized customers from placing orders into the system.

A data entry module 105 accepts data that has been input manually or automatically into the customer system. It should be realized that this data entry module preferably accepts data directly from integrated or third party oligonucleotide analysis software programs that are commercially available. These third party programs are used by customers to determine the proper oligonucleotide sequence to be synthesized.

Oligonucleotide data is then fed into an analysis module 115 which confirms that the nucleic acid sequence and composition provided by the data entry module will produce the desired oligonucleotide. The data analysis module is fed chemical bond information by a bond database 118 so that all of the potential bond types are analyzed by the analysis module 115. In addition, information on labels or other options can also be included. Examples of types of oligonucleotide information is provided below:

Examples of Oligonucleotide Options

Guaranteed Oligos™	All oligos are deprotected, desalted, PAGE controlled, additional purifications (PAGE, RP-HPLC) available	
DNA	Non-labeled	
	Fluorescent Labels	Fluorescein, 6-Fam, Hex, Tet, CY-5, CY-3, Texas Red, Rhodamine, Tamra, Rox, Dabcyl, Bi-fluorescent probes, plus many more
	Non-Fluorescent Labels	Digoxigenine, Biotin, Amine, Phophate, Thiol, Psoralen, Cholesterol, plus many more
	Other Modifications	Inosine, Nitroindole, dU, BrdU, BrdA, BrdG, IdU, IdC, FdU, TEG spacer, Etheno dA, C5-Propyne dC/dU, 5-Methyl dA/dC, 6-Methyl dG/dA/dT, 8-oxo dG/dA, 7-deaza dG/dA, ddA, ddC, plus many more
	LightCycler™ Hybridization Probes	Oligo 1 : 3' fluorescein Oligo 2 : 5' Red 640 - 3' Phosphate Oligo 2 : 5' Red 705 - 3' Phosphate
S-Oligos	Non-labeled	
	Fluorescent Labels	Fluorescein, 6-Fam, Hex, Tet, CY-5, CY-3, Texas Red, Rhodamine, plus many more
	Non-Fluorescent Labels	Digoxigenine, Biotin, Amine, Phophate, Psoralen, Cholesterol,
	Other Modifications	Inosine, Nitroindole, DesoxyUridine, plus many more
RNA/2'O-methyl		
Mixed Oligos		
Mass Oligos™	All oligos are deprotected, desalted and delivered at adjusted concentration	
	Mass Oligos™	orders of 24, 48, 72, 96...192...576...1152...5760...
	Mass Oligos™ 24 Hours	Order today before 10 a.m. and get them tomorrow before 10 a.m!
Bulk Oligos™	from 10 mg to 10 g, standard or purified, produced under GMP guidelines	
DNA	Non-labeled	
	Labeled	Fluorescein, Biotin, Amine, Phosphate, plus many more
S-Oligos	Non-labeled	

	Labeled	Fluorescein, Biotin, Amine, Phosphate, plus many more

Once all of this data has been analyzed, it is sent to a standard data conversion module 120 that converts all of the oligonucleotide data into a standard data format 125. One example of a preferred format for the standard data format 125 is and XML document, as shown below.

Information sent from the standard data format conversion module 120 concerns Bid requests and actual orders for oligonucleotides. Thus, from the customer's point of view, there are two possible scenarios: 1) The customer sends directly an order to the vendor "without quote", that means without having sent a bid request before and 2). The customer sends first a bid request, then, after receiving an answer from the vendor(s), sends the order "with quote". Accordingly, three possible functions need to be addressed:

- Order "without quote"
- Bid request
- Order "with quote"

Several types of information can be sent by the standard data format conversion module to the transaction server (and vendor).

a) The customer description (name, addresses, ..) and/or identification
b) The order and/or oligonucleotide "parameters": packaging, form, shipment, ...
These "parameters" may concern only orders, only oligonucleotide, or both.
c) The oligonucleotides complete description (only for orders)
d) The oligonucleotides partial description (only for bid requests)

The determination of how much information to send is preferably as follows:

- Order "without quote":
  a), b) and c)
- Bid request
  a), b) and d)
- Order "with quote":
  As a) and b) have been sent before with the bid request, it should only be necessary to send c) and the "quote" identifier are mandatory

The information for the four types (a), b), c) and d)) defined above are described below. Information is described as structures with "element" relationships of the structures denoted by "|-- ".

Customer information

Name	Type, List of values	Remarks
Customer		
|-- UniqueIdentifier		

|-- Contact		
|--|--Name		
|--|--Phone numbers		How many? 2 + fax?
|--|--Email		
|-- *Client Id*		Depends on supplier. Could be replaced by a Player unique id, but in all the cases, we should provide a way to send to a supplier the link (Player Id, Client Id)
|-- Ship-to address		
|-- Bill-to address		

Order and Oligonucleotide parameters

Name	**Type, List of values**	**Remarks**
Parameters		*?*
|-- Packaging		
|--|-- Type	Tube, Plate	
|--|-- Format	96, 384	Only if Type=Plate
|--|-- Aliquot		
|-- Form		
|--|-- Type	Suspended in liquid, Dry	• Autre terme plus précis que "Form"? • Could the packaging depend on the form?
|--|-- Liquid	Water|Other	Only if Type=Liquid
|--|-- Adjusted Concentration		Only if Type=Liquid
|--|--|-- Unit	Micromole, microgr/microl	
|--|--|-- Value		
|-- SystematicQualityControl	Yes, No	The Oligo supplier should return information on the Quality Control it will use
|--Application		
|--|-- Type	PCR, Sequencing, Hybridizations, Cloning	
|--|-- IntendedReactionsNumber	Integer	number or intended usage reactions possible
|--Purity	Standard, High, VeryHigh	The supplier should precise the method
|-- Shipment	Standard, Express	Only for orders
|-- Documentation		Only for orders

|--|-- Doc Type	technical data, quality certificate, instructions for use, etc	Can be multi-valued
|--|--Doc Delivery Form	Paper, Email, ...	Can be multi-valued

Most of these parameters can be sent to the transaction server only once, at the order stage, and applied to all the oligonucleotides. They can also be set explicitly for each oligonucleotide.

"Order" oligonucleotide description

Name	Type, List of values	Remarks
Oligo		
|-- Name	String, max length=19, no blanks	
|-- ExtraName	String	
|-- Quantity		Quantity could be omitted and calculated by the supplier from the Application fields
|--|-- Unit	OD, nmoles, micrograms	Depends on supplier
|--|-- Value	Integer	
|--PlatePositioning	(x, n) where x is a caps letter and n a number	Only if Packaging.Type= Plate. Max values for x and n depends on the plate size
|--Parameters		See below, optional. Could be defined at the order level
|--Sequence	See below	

b. Sequence description

i. The sequence structure:

- "extremity": 5', by default
  The extremity could be "modified". In this case, it is called "Modifier 5'" (or "Modifier 3'")
- A sequence of { <monomer>, <link>, <monomer>,<link>, ... <link>, <monomer>}
- "extremity": 3'

ii. Monomer Description

There are 3 kind of monomers:

- Bases:

The letters authorized for entry are: A , C , G, T , U, I, R, Y, M, K, S, W, H, B, V, D, N to which are added, according to the international code for degenerate bases (i.e. when the customer user desires a mix of two, three or four bases at a position):

R corresponding to *(A, g)*

Y	corresponding to	*(C, T)*
M	corresponding to	*(A, C)*
K	corresponding to	*(g, T)*
S	corresponding to	*(g, C)*
W	corresponding to	*(A, T)*
H	corresponding to	*(A,T,C)*
B	corresponding to	*(g,T, C)*
V	corresponding to	*(g, A, C)*
D	corresponding to	*(g, A, T)*
N	corresponding to	*(A, C, g, T)*

- Spacers
  C3 (propyl)
  C9 (triethylene glycol)
  C12 (tetraethylene glycol)
  C18 (hexaethylene glycol)
  OTHER : To be specified by the customer

- Modifiers

Bases could be described in 2 ways:
By type and value

- Value: A, C, g, T, N
- Type: ADN, ARN, 2'O-Methyl, Other
-

Or by strings:

- A, C, g, T... for ADN
- rA, r C, rg, U for ARN
- oA, oC, og, oT for 2'O-Methyl
-

This second format is more usual, but might be too restricted if we want to deal with new types of monomers. For this reason, the first format is preferred.

Spacers and Modifiers

Name	**Type, List of values**	**Remarks**
Base		
|-- Type	ADN, ARN, 2'O-Methyl, "Other"	
|-- Value	A, C, g, T, N, I	
Spacer	C3, C9, C12, C18, *OTHER to be specified by the customer*	
InternalModifier	Biotin-dT, Digoxygenin, Fluorescein-dT, Texas Red,	

	Rhodamine, Tamra, Rox, Joe, Red640, Dabcyl, *OTHER to be specified by the customer*	

iii. Describing links

We describe here only links between bases. A link can be described by a type:

- Phosphodiester (by default)
- Phosphorothioate
- Methylphosphonate
- OTHER : To be specified by the customer

Link Types

Name	Type, List of values	Remarks
Link	Phosphodiester , Phosphorothioate, Methylphosphonate, *OTHER to be specified by the customer*	

Example of Sequence Data in XML format

Name	Type, List of values	Remarks
Sequence		
|-- Extremity5		
|--|--Modifier5	Modifier name	Optional
|--MonomersAndLinks	(Monomer,Link)+, Monomer)	That means { <Monomer>, <Link>, <Monomer>,<Link>, ... <Link>, <Monomer>} Wher Monomer = Base|Spacer| InternalModifier
|-- Extremity3		
|--|--Modifier3	Modifier name	Optional

Preferably, for confidentiality and security reasons, the exact sequence descriptions will not be send at bid request time. Thus, we have to decide what are the minimal parameters that are

required in order to calculate the price and, in some circumstances, the fabrication and shipment delay times.

Accordingly, we obtain for the oligonucleotide sequence:

- Number (Nb) of bases by type:
  - Nb of A, C, G, T (global sum)
  - Nb of degenerate bases (N, X, Y...)
  - Nb of Inosines
  - Nb of ADN bases
  - Nb of ARN bases
  - Nb of 2'O-Methyl bases
  - Nb of "Other" bases ("Other" must be specified)
- Nb and type of internal modifiers:

Nb for each type

- Nb of spacers
  - Nb of C3 (propyl)
  - Nb of C9 (triethylene glycol)
  - Nb of C12 (tetraethylene glycol)
  - Nb of C18 (hexaethylene glycol)
  - Nb of Other" ("Other" must be specified)
- Nb and type of non-standard links:
  - Phosphorothioate
  - Methylphosphonate
  - Nb of "Other" ("Other" must be specified)
- Modifier 5'? If yes, type
- Modifier 3'? If yes, type

For convenience, only fields that have data are preferably sent to the transaction server and vendor.

Example of Bid XML Data

Name	**Type, List of values**	**Remarks**
OligoCharacteristics		
|-- Name	String, max length=19, no blanks	
|-- ExtraName	String	
|-- Quantity		Quantity could be omitted and calculated by the supplier from the Application fields
|--|-- Unit	OD, nmoles, micrograms	Depends on supplier
|--|-- Value	Integer	
|--PlatePositioning	(x, n) where x is a caps letter and n a number	Only if Packaging.Type= Plate. Max values for x and n depends on the plate size
|--SequenceCharacteristics		

|--|-- NbOfStandardBases	Integer	Nb of A, C, G, T (global sum)
|--|-- NbOf*Degenerescences*	Integer	Nb of N, X, T ....
|--|--NbOfInosines	Integer	Nb of I
|--|--NbOfADN	Integer	
|--|--NbOf2OMethyl	Integer	
|--|--OtherBasesTypes	List	
|--|--|--Type		"Other" definition
|--|--|--Number	Integer	
|--|-- NbOfInternalModifiers	Integer	
|--|--NbOfC3	Integer	
|--|--NbOfC9	Integer	
..... *to be completed*		

Example of Order "without quote" XML Data

Name	**Type, List of values**	**Remarks**
OrderWithoutQuote		
|--Identifier	Unique Identifier	
|--Customer	See 0	
|-- Parameters	See 0	
|--Oligonucleotide	List of Oligonucleotide	
|--|--Oligo	See 0	

Example of Bid Request XML Data

Name	**Type, List of values**	**Remarks**
BidRequest		
|--Identifier	Unique Identifier	
|--Customer	See 0	
|-- Parameters	See 0	
|-- OligonucleotideCharacteristics	List of OligoCharacteristics	
|--|-- OligoCharacteristics		

Example of Order "with quote" XML Bid Data

Name	**Type, List of values**	**Remarks**
OrderWithQuote		

|--Identifier	Unique Identifier	
|--BidReplyIdentifier	Unique Identifier	Identifier returned by the supplier
|--Oligonucleotide	List of Oligonucleotide	
|--|--Oligo	See 0	

Illustrated below is one example of an XML oligonucleotide order that is sent from the Standard data format conversion module. Of course, alternative XML formats could be substituted without affecting the overall functioning of the system.

```
<Order>
    <Customer>
        <Contact>
            <Name>customer name</Name>
            <Phone>phone number</Phone>
            <Fax>fax number</Fax>
            <Email>email address</Email>
        </Contact>
        <ShipToAddress>
            <Name>organization name</Name>
            <Address>organization address</Address>
            <City>organization city</City>
            <ZipCode>organization city</ZipCode>
            <Country>organization country</Country>
        </ShipToAddress >
        <BillToAddress>
            ..... see the ShipToAddress
        </BillToAddress>
    </Customer>
    <OrderDescription>
        <Packaging>
            <Type>Tube</Type>
            .....
        </Packaging>
        <Form>Liquid</Form>
        <Shipment>Express</Shipment>
        ....
    </OrderDescription>
    </Oligonucleotide>
        <Oligo>
            <Name>PPAR01</Name>
            <Quantity>
            <Unit>OD</Unit>
            <Value>5</Value>
            </Quantity>
            <Purity>NO</Purity>
            <Sequence>
                Extremity could be omitted if default
                <BaseElement>C</BaseElement>
                Link could be omitted if default (to be checked)
                <BaseElement>T</BaseElement>
                <BaseElement>G</BaseElement>
```

```
                    <BaseElement>A</BaseElement>
                    <BaseElement>A</BaseElement>
                    <BaseElement>C</BaseElement>
                    <BaseElement>C</BaseElement>
                    ....
                </Sequence>
            </Oligo>
            .....
        </Oligonucleotide>
    </Order>
```

Once the customer system transmits the standard data format 125 to the transaction server, it waits to receive a standard data format back indicating the status of the inquiry. Thus, a standard data format reception module 130 within the customer system reads incoming standard data formats and displays the received data through a standard data format display module 135.

The customer system is preferably associated with custom chemical analysis programs that help the customer design the appropriate molecule. For example, if the customer wants to design an oligonucleotide that uniquely binds to a particular fragment of DNA, software programs exist for determining unique short stretches of DNA within the particular fragment. Such programs, for example, are available on the Internet at http://www.gcg.com from the University of Wisconsin Genetics Computer Group.

c. Transaction Server

The Transaction server is illustrated in Figure 3, and includes a collection of executable software programs and databases that link to the Vendor's (or exchange vendor's) information system and regulates the interactions between the customer, the Administration, the Suppler and the Manufacturer.

As illustrated, the transaction server includes a bid interface module 200 for receiving and processing XML formatted bid requests from customers. Within the bid interface module 200 is an authentication module 202 that provides secured access to the transaction server from the customer system. Data that is sent from the customer system is preferably encrypted by conventional public key/private key infrastructure methods, or other ciphers that are well known in the art.

The XML documents from the customer system are logged into a bid tracking module 205 that includes commands and data storage for tracking the progress of a particular bid after it has been sent to a plurality of vendors through a vendor bid interface module 210. Integrated with the vendor module 210 is an encryption module 212 that provides secured access to each vendor system.

Once the bid has been sent to a plurality of vendor systems, the transaction server waits until each vendor system returns an XML formatted bid response. Of course, some vendor systems

may not bid on producing the desired product, so timeout features allows the transaction server to return a set of bids to the customer even if all of the vendor system has not returned a bid.

Each bid that is returned to the transaction server is decrypted by the encryption module 212 and then forwarded to a bid compilation module 215 which reads the XML bid data and orders each bid according to a predefined criteria. For example, most customers would want the bids ranked in order of price, however the system could also provide rankings according to speed of delivery, purity of compound or other factor desired by the customer. Once the bid compilation module 215 has received and ranked each bid, the bids for the customer are formatted back into an XML format at an Standard data format conversion module 220 and then transmitted to the customer.

If a customer decides to accept one of the bids, a purchase order is thereafter received by an order module interface 225 in the transaction server. The order, as discussed above, includes all of the data necessary for the vendor to synthesize the custom oligonucleotide. In order to maintain security for the order, it is preferably send through an authentication module 227 which verifies the identity of the ordering customer through, for example, an authorized digital certificate. Once the data has been received by the order module interface, it is logged into an order tracking module 230 that tracks the status of all orders in the system. The order is then sent through a vendor order module interface 235 to the designated vendor so that the custom compound will be synthesized.

Once the compound has been synthesized, the vendor order module interface 235 returns order information to a transaction processing module 240 that completes any necessary post-production processing. For example, the transaction processing module can include an internal or external accounting system for directly billing the customer for the custom product. The transaction processing module can also notify the customer of the status of the completed order, with, for example, shipping tracking numbers or other relevant information.

In particular, the Transaction server allows, without limitation, to save temporarily information, data or queries received from any of the Administration, Manufacturer or customer modules while the recipient is not connected and keep them available until its next connection. Thus, the transaction server includes modules that perform the following features:

- The authentication of the customer.
- The processing of bid requests received from customers.
- The real time quote calculation.
- The transmission of quotes to customer.
- The reception of orders from customers.
- The transmission of order tracking info to customers.
- The automatic editing of invoices.
- The transmission of invoices to Administration.
- The collection of electronic payments.

d. Administration System

The Administration system 20 includes executable software and is mainly used in an interactive connected mode to perform through the Transaction server to communicate tasks between the Administration's information system, the vendor system and the customer system.

The administration system preferably includes modules that perform the following functions:

- The processing of PO Request.
- The transmission of PO approvals and numbers.
- The receipt of invoices.
- Checks and necessitates partial shipments of orders in receipt for payment of invoices
- The transmission of electronic payments.

e. The Vendor System

Referring to Figure 4, one example of a vendor system 35 is illustrated. The vendor system 35 includes a series of programs/commands and modules for performing the various necessary functions outlined below.

Within the vendor system 35 is a transaction server interface 300 that accepts incoming XML documents from the transaction server 30 and converts those documents into data formats that are read by the remaining modules of the vendor system. If the incoming document is a bid request, the request is sent to the vendor bid module 40.

Linked to the vendor bid module 40 are several databases and data storages that are used to price the various custom compounds that are being bid by the customers. For example, a contract pricing database 310 holds the name of customers and whether any special pricing rules apply to those customers. Thus, customers that order large quantities of products can be given special pricing by reference to the contract price database. The proper price for a customer is determined by first comparing a unique customer identifier that was sent by the customer to a customer database 315. The customer database can then determine the proper pricing options for that customer by linkage to the contract price database 310. For example, a first customer might be granted contract pricing from the "Group A" contract price sheet, whereas a second more regular customer might be granted contract pricing from a lower priced "Group B" contract price sheet.

Of course there is also a standard price database 320 that contains the standard prices for each component in the custom oligonucleotide. If a customer does not have a contract price, or there is no contract price for a particular compound in the contract price database 315, the price is retrieved from the standard price database 320. Examples of pricing for various oligonucleotide components are illustrated below.

Examples of Pricing for Oligonucleotide Components

MASS OLIGOS	All oligos are fully deprotected, desalted, statistically controlled and quantitated at 260 nm. Must be ordered in multiples of 24 oligos. .	
	2 OD	$.70/base
	5 OD	$.80/base
STANDARD OLIGOS	All oligos are fully deprotected, desalted, systematically PAGE controlled and quantitated at 260 nm.	
	2 OD (typical yield 2-4 OD)	$.75/base
	5 OD (typical yield 5-8 OD)	$0.95/base
	10 OD(typical yield 10-12 OD)	$1.65/base
	50 OD	$4.00/base
	100 OD	$7.45/base
(No charge for degenerate bases.)		
PURIFIED OLIGOS	All oligos are fully deprotected, desalted, PAGE/HPLC purified and quantitated at 260 nm.	
PAGE	1 OD	$1.65/base + $65.00/purification (for <50mers), $90.00/purification (for >50mers)
HPLC	10 OD	$4.00/base + $90.00/purification (for <50mers), $125.00/purification (for >50mers)
	50 OD	$7.45/base + $150.00/purification (for <50mers), $175.00/purification (for >50mers)
	100 OD	$14.00/base + $175.00/purification (for <50mers), $200.00/purification (for >50mers)
5' MODIFIED OLIGOS		
Standard, Modified Oligos		
Biotin	5 OD	$0.95/base + $35.00/modification
	10 OD	$1.65/base + $50.00/modification
Fluorescein	5 OD	$0.95/base + $40.00/modification
	10 OD	$1.65/base + $55.00/modification
6-FAM, HEX, TET	5 OD	$0.95/base + $55.00/modification
	10 OD	$1.65/base + $75.00/modification
Amine	5 OD	$0.95/base + $30.00/modification
	10 OD	$1.65/base + $40.00/modification
Phosphate	5 OD	$0.95/base + $25.00/modification
	10 OD	$1.65/base + $45.00/modification
Thiol	5 OD	$0.95/base + $55.00/modification
	10 OD	$1.65/base + $70.00/modification
Purified, Modified Oligos		
Biotin	1 OD	$1.65/base + $65.00/purification + $50.00/modification
	10 OD	$4.00/base + $90.00/purification + $100.00/modification

Fluorescein	1 OD	$1.65/base + $65.00/purification + $55.00/modification
	10 OD	$4.00/base + $90.00/purification + $110.00/modification
6-FAM, HEX, TET (ABI dyes)	1 OD	$1.65/base + $65.00/purification + $75.00/modification
	10 OD	$4.00/base + $90.00/purification + $180.00/modification
ROX, TAMRA (ABI dyes)	1 OD	$1.65/base + $65.00/purification + $55.00/modification
	10 OD	$4.00/base + $90.00/purification + $150.00/modification
CY5, CY3	1 OD	$1.65/base + $65.00/purification + $55.00/modification
	10 OD	$4.00/base + $90.00/purification + $140.00/modification
Rhodamine	1 OD	$1.65/base + $65.00/purification + $55.00/modification
	10 OD	$4.00/base + $90.00/purification + $140.00/modification
Texas Red	1 OD	$1.65/base + $65.00/purification + $55.00/modification
	10 OD	$4.00/base + $90.00/purification + $140.00/modification
Digoxigenin	1 OD	$1.65/base + $65.00/purification + $85.00/modification
	10 OD	$4.00/base + $90.00/purification + $220.00/modification
Amine	1 OD	$1.65/base + $65.00/purification + $40.00/modification
	10 OD	$4.00/base + $90.00/purification + $80.00/modification
Phosphate	1 OD	$1.65/base + $65.00/purification + $45.00/modification
	10 OD	$4.00/base + $90.00/purification + $90.00/modification
Thiol	1 OD	$1.65/base + $65.00/purification + $70.00/modification
	10 OD	$4.00/base + $90.00/purification + $140.00/modification
PHOSPHOROTHIOATES		
Standard Oligos	10 OD	$2.65/base
	50 OD	$5.25/base
	100 OD	$8.95/base
Purified Oligos	1 OD	$2.65/base + $65.00/purification
	10 OD	$5.25/base + $90.00/purification
	50 OD	$8.95/base + $150.00/purification

	100 OD	$16.00/base + $175.00/purification
(For mixed backbone oligos PS/PO, use price per base for respective linkage)		
LightCycler™ PROBES		
0.3 nmol (100 reactions)	Oligo 1(Fluorescein 3')	$70.00/oligo
	Oligo 2 (Red Dye 5' and Phosphate 3')	$210.00/oligo
	Oligo 1 + 2	$255.00/set
1.0 nmol (300 reactions)	Oligo 1(Fluorescein 3')	$110.00/oligo
	Oligo 2 (Red Dye 5' and Phosphate 3')	$255.00/oligo
	Oligo 1 + 2	$330.00/set
3.0 nmol (1000 reactions)	Oligo 1(Fluorescein 3')	$150.00/oligo
	Oligo 2 (Red Dye 5' and Phosphate 3')	$285.00/oligo
	Oligo 1 + 2	$383.00/set
30 nmol (10,000 reactions)	Oligo 1(Fluorescein 3')	$485.00/oligo
	Oligo 2 (Red Dye 5' and Phosphate 3')	$1033.00/oligo
	Oligo 1 + 2	$1416.00/set
Expression Analysis Primers		
10 OD HPLC purified		
T7-(dT)24 Primer: ggC CAg TgA ATT gTA ATA CgA CTC ACT ATA ggg Agg Cgg (dT)24		$279.00
Control Oligo B2: b gTC gTC AAg ATg CTA CCg TTC Agg A		$265.00

Once a price has been calculated based on the number of bases, types of linkages, and other features of the requested oligonucleotide, that price is converted into a predetermined XML format, as described above, and transmitted through the transaction server interface 300 to the transaction server.

If the bid is accepted by the customer, a purchase order (in XML format) is forwarded through the transaction server to the transaction server interface in the vendor system. It should be realized that the vendor system preferably stores a reference (bid identifier) to previous bids so that any new orders can reference a bid that was made. This ensures that the proper price is charged for the ordered product. Once the transaction interface module receives the new order, the order is sent to the vendor order module 37. This module includes an order database 330 that stores each new order coming into the system. In addition, an order tracking module 335 within the vendor order module provides the customer and the transaction server with updated information on the status of the order.

Linked to these aforementioned modules is a vendor accounting system 340 that is responsible for receiving the incoming purchase order, and billing the customer or host of the transaction server for production of the custom oligonucleotide. The accounting system can be a custom designed system, but is preferably based on one of the standard billing, ordering,

purchasing, tracking and reporting systems widely available through vendors such as SAP, Oracle and others.

The vendor order module 37 also includes a production module 350 that reads the incoming XML production data from the transaction server and sends a production order to a data conversion module 355. The data conversion module 355 converts the XML order data into a data format that is appropriate for synthesis on a nucleic acid synthesizer, such as a PE Biosystems (Foster City, CA) Model ABI 3948 Nucleic Acid Synthesis and Purification System.

Once the data has been converted into the proper format for transfer to a synthesizer, it is forwarded to a synthesizer interface module 360 which is linked to the synthesizer.

f. Order Oligonucleotides

Referring now to Figure 5, one embodiment of the process 400 for ordering oligonucleotides is illustrated. Although this process is illustrative of ordering oligonucleotides, similar processes can be used to order other custom biologicals.

The process 400 begins at a start state 402 and then moves to a state 404 wherein oligonucleotide data is received in the customer system. For example, the oligonucleotide data might be received through the player software described previously.

Once the oligonucleotide data has been received by the customer system at the state 404, the process 400 moves to a decision state 410 to determine whether a bid has been requested by the customer. If a bid has been requested, the data is converted into an XML format at a state 412. The process 400 then moves to a state 414 wherein the XML data is transmitted from the customer system to the transaction server. As discussed previously, this transmission preferably includes encrypting the data as it is sent to the transaction server. The process 400 then moves to a state 416 wherein the transaction server forwards bid requests in XML format to a plurality of vendors so that each vendor can respond to the big request. Similarly, the transaction server preferably encrypts the data sent to the each vendor so that unauthorized individuals cannot determine what molecules are being ordered or bid by a particular customer.

The process 400 then moves to a process state 418 wherein each vendor determines a price for the oligonucleotide order they have received. This process of pricing oligonucleotides is described more specifically with reference to Figure 6.

Once the oligonucleotides have been priced, the process 400 moves to a state 422 wherein the prices from each vendor are converted into an XML document and transmitted to the transaction server. The transaction server then compiles each of the bid prices from each vendor at a state 424. The bids, as described above, can be listed by vendor identifier, price, delivery date or any other data type. The process 400 then moves to a state 426 wherein the bids are forwarded from the transaction server to the customer systems.

A determination is then made at a decision state 428 whether any bid was accepted by the customer. If a bid was accepted by the customer, the process 400 moves to a process state 430 in order to process the order for the custom oligonucleotides. The process state 430 is described in more detail with reference to Figure 6 below.

The process 400 then moves to a state 432 wherein an invoice is received by the customer from the selected vendor that has been chosen to process the order. The process 400 then terminates at an end state 434.

It should be realized that if a bid is not requested at the decision state 410, the process 400 moves directly to the process state 430 so that the customer can immediately order the desired product from a desired vendor.

Referring now to Figure 6, the process 418 of pricing oligonucleotides is described in more detail. The process 418 begins at a start state 450 and then moves to a state 452 wherein the XML data corresponding to the number of nucleotide bases, types of modifications to the ordered oligonucleotide, specific linkages between oligonucleotides and other features of the oligonucleotide sequence are received by the vendor systems. It should be realized that this process is normally undertaken by several vendors simultaneously in order to provide a variety of prices to the customer.

The process 418 then moves to a state 454 wherein the identity of the customer ordering the oligonucleotide is identified. The process 418 then moves to a state 456 wherein the specific pricing data for the identified customer is retrieved from a customer pricing database. The number of bases within the oligonucleotides sequence, identification of spacers and internal modifiers and other features of the sequence are then determined at a state 458 by the vendor system. A determination is then made at a decision state 464 whether custom pricing has been found for the particular customer that is ordering the product. If custom pricing is found, that price is retrieved from a customer pricing database at a state 470. The sum of all prices for each component of the oligonucleotide sequence is then determined at a state 472 and the process 418 terminates at an end state 476.

It should be realized that if a determination is made at the decision state 464 that a custom price list is not found, the process 418 moves to a state 478 wherein standard pricing for each component of the ordered oligonucleotide product is retrieved from a database. The process 418 would then continue at the state 472 wherein the sum of all prices for the oligonucleotide is determined.

Referring now to Figure 7, the process 430 of processing an order from a customer to a vendor is illustrated. The process 430 begins at a start state 500 and then moves to a state 502 wherein a XML order is transmitted by the customer to the selected vendor that has provided the

appropriate bid. The process 430 then moves to a state 504 wherein a new order file is opened by the vendor within their vendor order database.

The order is then transmitted to a production module at a state 506. In order for the oligonucleotide to be processed, it is preferably converted from the XML format into a data format that is compatible with the synthesizer that will create the actual oligonucleotide sequence. Thus, at a state 510 the XML document is converted into a synthesizer compliant data format so that it can be immediately transmitted into a conventional oligonucleotide. Of course, it should be realized that a similar scheme could be utilized for ordering custom peptides, wherein the XML document is converted into a file format that is compatible with a protein synthesizer.

The data is then transmitted to the nucleotide synthesizer at a state 512. A determination is then made at a decision state 516 whether the oligonucleotide has been completely synthesized.

Once the order has been completed, the process 430 moves to a state 520 wherein an order tracking module within the vendor system is updated to indicate that the oligonucleotide sequence has been completely synthesized. The process then moves to a state 524 wherein the accounting system within the vendor system is updated to indicate that the order has been completed and the customer's bill can be generated.

The process 430 then moves to a decision state 526 to determine whether the product has been shipped to the customer. Once the produce has been shipped, the order tracking module is updated at a state 530 to indicate that the order is in transit to the customer. An invoice is then transmitted either electronically or via paper to the customer at a state 532. The process then terminates at an end state 534.

5. Features of the Oligonucleotide "Player"

In one embodiment, the customer computer 15 includes a polymorphic "player" program that manages communication between the various systems. Using the player, the customer system is used in a stand-alone local mode disconnected from any external system, or in a connected mode where it manages communication with one or several external systems. The customer system, as described above, includes bid and order modules which are compiled and displayed in the player so that the player appears on the customer's computer screen under different shapes depending on the task it is required to perform. This player provides an intuitive interface for inputting and manipulating ordering data. Three basic shapes correspond to the three basic functioning status of the player.

- The Icon shape corresponding to the idle status.
- The console shape corresponding to the mode selection status.
- The screen shape corresponding to the different working modes.

The navigation from one status to another is always possible by different types of actions on the mouse or on the keyboard. In the Idle Status mode, the player is not active. However, if it is connected to the transaction server, it works as a passive receiver. If and when information is received, a colored indicator flashes in the center of an icon to inform the customer that information is ready to be read. The customer can activate the player and access the selection status by clicking their mouse cursor on the flashing indicator.

In the selection status, the player appears under the familiar design of a game console. By simple mouse cursor displacement on the console, a choice of functional modes appears on a virtual lid. A click on the lid allows access to the screen status related to the functional mode displayed on the lid.

The choice of accessible functional modes includes without limitation:

- "Create Order" Mode
- "Edit Order" Mode
- "Bid Request" Mode
- "Send Order" Mode
- "Order Status" Mode
- "Tool Box" Mode

The selection of any of the above functional modes opens the screen status in the selected functional mode. Of course it should be realized that other configuration functionalities are accessible by menus in the selection status by a simple click on designated buttons. These functionalities include without limitations the setting-up of the Customer Profile and Preferences.

a. Player

Referring now to Figure 8, one embodiment of a player 600 is illustrated. As discussed previously, the player 600 is a "polymorphic" program that changes shapes depending on its status. As illustrated in Figure 8, the player is in an idle mode which resembles a small oval shape. At the center of the oval is an indicator 602 which changes colors depending on the status of orders within the system. For example, if desired information has been received, the indicator 602 might flash red. However, in all other circumstances, the indicator might be a steady yellow color.

Along with the indicator 602 are a series of indicator lights that illustrate buttons that are used in other modes of the player device.

Referring now to Figure 9, an illustration of the player 600 in its selection mode is shown. When the player is in the selection mode, each of the buttons 604, 606, 608, 610, 612 and 614 are enabled so that clicking a mouse on each button will open the corresponding display screen.

Beginning from the left is a create order button 604 which causes the player to enter the mode illustrated below in Figure 10. In addition, the player 600 includes a edit order button 606

which causes the player to enter the mode illustrated in Figure 11. The player 600 also includes a bid request button 608 which results in the player entering the mode illustrated in Figure 12.

Also within the player 600 is a send order button 610 which transmits pending orders to the transaction server. An order status button 612 is also provided which retrieves a screen illustrating the status of pending orders as illustrated in Figure 13. Note that in this polymorphic shape a text display 620 for displaying the mode selected by the mouse is shown.

If the create order button 604 is depressed by the customer, the create order display window, as shown in Figure 10, is opened to the customer. As illustrated, the create order window includes a text box 650 for entering text corresponding to the oligonucleotide sequence that is to be ordered. In addition, display boxes 652 and 653 show the order number and oligonucleotide name for the present order being modified.

As text is entered into the text box 650, it is converted into a graphical representation of the oligonucleotide sequence and displayed in the graphical output box 656. As shown, each nucleotide of the sequence is displayed graphically by a different color and shape. In addition, the label of each nucleotide is provided within the graphical element corresponding to the particular nucleotide. For example, the nucleotide sequence TAG is illustrated as a first graphical element 658 which provides a label of a letter "T" in the center. Connected to the graphical element 658 is a straight graphical line 660 which connects to a second graphical element 662 which provides a label of a letter "A" in the center. The graphical 662 is connected through a straight graphical bar 664 to a third graphical element 668 which provides a label of a letter "G" in the center. Thus, through the use of these graphical illustrations and elements, the nucleotide sequence entered in the text box 650 is graphically displayed to the user.

As shown by the jagged line 670 disposed between a graphical element 672 and a second graphical element 676, various linkages between nucleotide sequences are illustrated in the graphical window 656. By displaying varying linkages through different graphical objects, the customer can easily determine the format of the nucleotide sequence and whether any modifications to the linkages are provided.

Note that a sound indicator 680 is provided on the create order screen which results in a voice synthesized output of the nucleotide sequence, including all modifications to that sequence. The process of outputting voice is illustrated below in Figure 15.

Referring now to Figure 11, an edit order display screen 700 is shown. The edit order display screen 700 is activated by depressing the edit order button 606. As shown, a table 704 is provided in the display screen 700 which lists the sequence number, name, base number, utilization, priority and nucleotide sequence of oligonucleotides that have been ordered. As to be imagined, selecting, for example, line 706 will return the customer to the create order display shown in Figure 10. This would allow the customer to edit any orders prior to being sent out for a bid.

Referring now to Figure 12, a bid request display 750 that is activated by the bid request button 608 is illustrated. As shown, the bid request display 750 includes a table 754 having the following categories: selected, ID number, name, creation date, oligo number, utilization, priority, and number of bases. The selection field 756 provides checkboxes which indicate which of the ordered oligonucleotides should be sent out for a bid. Thus, the customer chooses which of the ordered oligonucleotides should be bid by selecting checkboxes 756 corresponding to the proper oligonucleotides. The customer can then press the send order button 610 to begin the process of transmitting bid requests to the various vendors.

It should be realized that the send order button 610 can provide options for which vendors, or groups of vendors, should receive the bid requests. This allows the customers to designate certain vendors as preferred over other vendors within the system.

Referring now to Figure 13, an order status display screen 800 that is activated by the button 612 is illustrated. As shown, within the order status display screen 800 is a table 802 which lists each of the orders that have been sent out for bid. Within the table 802 are fields for the oligonucleotide identifier, name, creation date, oligonucleotide number, utilization, and quote number for each oligonucleotide that has been ordered.

In addition, selecting a particular order within the table 802 results in a detailed display of the status on that order within a table 804. For example, the table 804 shows the status of each order as it progresses through the system. In addition, indicators 806 provide graphical indicia of the status of a particular order. For example, when an order has been sent but not received, the indicator 806 might be green. However, once a bid has been received, the indicator might turn yellow. Thus, a customer can visually determine the status of each order within the system.

Referring now to Figure 14, a process 900 of creating an oligonucleotide using the create order display (Figure 10) is illustrated. The process 900 begins at a start state 902 and then moves to a state 904 when the order entry screen is displayed to the customer. A determination is then made at a decision state 906 whether a new nucleotide has been entered into the nucleotide text box. If a nucleotide was not entered, the process 900 moves to a decision state 908 to determine whether a modified base has been entered into the system. As can be imagined, a modified base can be entered through a selection of menu choices that provide a series of base modifications. These modifications can then be illustrated graphically or through text to the customer.

If a determination is made that a modified base was not entered, the process 900 moves to a decision state 912 to determine whether a custom linkage has been entered in the system. A custom linkage can be provided between two nucleotide bases by selecting the appropriate linkage through a series of menu choices within the create order display window. If a determination is made that a custom linkage has not been entered, a determination is made at a decision state 916 whether any other element has been entered in the display window. Other elements can be various types of

modifications, labels, or other alterations to the nucleotide sequence that might make up part of an oligonucleotide order. If no other elements have been entered, the process terminates at an end state 920.

It should be realized that if a nucleotide had been entered at the decision state 906, the process 900 moves to a state 922 wherein the nucleotide that was entered is graphically displayed within the create order window. This graphical representation of the nucleotide base is provided to the customer so that the customer can easily identify the oligonucleotide that has been ordered. The process then terminates at the end state 920.

If a determination was made at the decision state 908 that a modified base had been entered, the process 900 moves to a state 926 wherein the modified base is displayed as a graphical object within the create order display. The graphical object could be, for example, of a different shape or color than the standard nucleotide base thereby providing an indicator to the customer that a modified base has been ordered. For example, if the normal base is displayed as a circle, the modified base might be displayed as a square. Once the modified base has been displayed on the create order display window, the process terminates at the end state 920.

If a determination was made at the decision state 912 that a custom linkage had been entered by the customer, the process 900 moves to a state 930 wherein the custom linkage is displayed as a graphical object on the create order display window. As discussed above, the custom linkage might be displayed as, for example, a curved, zigzag or jagged line between the graphical objects indicating oligonucleotide bases. Thus, a customer reviewing the order could easily determine that a custom linkage had been provided between two bases by the shape of the graphical line running between each base. In addition, varying colors can be used within the graphical indicator of the modified base to show differences between a standard linkage and a custom linkage. The process then terminates at the end state 920.

If a determination was made that another element was entered at the decision state 916, the process 900 moves to a state 934 wherein the appropriate graphical element indicating the chosen element is displayed to the customer. The process then terminates at the end state 920.

Referring now to Figure 15, a process 950 for outputting voice to the customer is illustrated. The process 950 begins at a start state 952 and then moves to a state 954 wherein the first nucleotide in the sequence is read by the system. As is known, several types of text readers are available that retrieve a string and, beginning at the first letter, output each letter of the string to a voice synthesizer.

Once the first nucleotide has been read at the state 954, a determination is made at a decision state 956 whether the nucleotide is a modified base or a standard base. If a determination is made that the nucleotide is a standard base, the process 950 moves to a state 958. The name of the nucleotide is output to the voice synthesizer. As is known, conventional voice synthesizers will

verbalize text that is sent to them by a program. Thus, sending the character "a" to the voice synthesis system will cause the computer to output the "a" sound through the computer speakers.

Once the nucleotide has been output to the voice synthesizer, the process 950 moves to a state 960 wherein the type of linkage between the currently output nucleotide and the next nucleotide is read. The process then moves to a decision state 962 to determine whether the linkage is standard or not. If the linkage is not standard, the process 950 moves to a state 964 wherein the proper voice text describing the nonstandard linkage is determined. Thus, for each modified linkage, the system stores the text equivalent of that linkage so that it can be output to the voice synthesis system. Once the proper text for the modified linkage is determined at the state 964, the text is output to the voice synthesizer at a state 966. A determination is then made whether other nucleotides are within the sequence at a decision state 968. If no more nucleotides are available in the sequence, the process terminates at an end state 970.

It should be realized that if a determination was made at the decision state 956 that a modified nucleotide was read, the process 950 moves to a state 972 to determine the appropriate text to output to the voice synthesis system to describe the modified base. Once the appropriate text has been determined, the process 950 returns to the state 966 to output the text to the voice synthesizer.

It should also be realized that if more nucleotides are available for analysis at the decision state 968, the process 950 moves to a state 974 to read the next nucleotide in the sequence.

E. Example 1

This example provides a description of one embodiment of a system for designing, ordering, pricing, tracking and directing production of custom oligonucleotides. This system relies on an "Oligoplayer" module that runs on the customer's computer and is intended for creating, editing, sending and managing orders for oligonucleotides. The OligoPlayer is a versatile module that can adapt to three possible states, the Standby Mode, the Console Mode and the Display Mode.

When the OligoPlayer is in Standby Mode (FIG. 8), it appears as an oval shaped icon displaying: (1) a central heart button/indicator 602, (2) six lights representing the available function modes 604, 606, 608, 610, 612, and 614, (3) a reduction button 616 and (4) a close button 618.

The Console Mode (FIG 9) offers the user access to all the function modes of the OligoPlayer. When the OligoPlayer is in Console mode it appears as an oval shaped icon displaying: (1) a text display screen 620, (2) a return to Standby Mode button 622, (3) a close button 618, (4) central heart indicator 602, (5) a reduction button 616, (6) six "keys", or functionality buttons, that allow the user to (a) create an order 604, (b) edit an order 606, (c) make a bid request 608, (d) send an order 610, (e) check an order's status 612, and (f) view toolbox 614.

II. Display Mode

The Console Mode can be converted into a Display Mode, which provides access to several features of the OligoPlayer. The Display Mode allows the user access to all of the functional modes, pass from one functional mode to another, and program the OligoPlayer. While in the Display Mode, the user has access to four other modes: (1) Create Order Mode, (2) Edit Order Mode, (3) Bid Request Mode and (4) Order Status Mode. In the Display Mode, the OligoPlayer displays: (1) a reduction button 616, (2) a close button 618, (3) an order zone 619, (4) a current functional mode display 621, (5) control paddles 623a, 623b, 623c, (6) tabs to access other functional modes 604, 606, 608, 610, 612, 614 and (7) a light that indicates new replies to bids 625.

Clicking on a functional mode tab with a mouse cursor will take the user into the corresponding functional mode. The tab that corresponds to the functional mode in current use will be green to distinguish it from the red tabs that are not in use. The control paddles 623a, 623b, 623c allow the user to access the following functionalities: (1) preferences, (2) profiles, (3) tools, (4) search, (5) return to the console mode.

Create Order Mode

FIG. 10 shows an illustration of the Create Order Mode, which allows the user to create an order. In this mode the OligoPlayer displays: (1) an order number display box 652, (2) an oligonucleotide ID display box 653, (3) navigation buttons 654a, 654b and wheels 656a, 656b for the order number display box, and the oligonucleotide ID display box, (4) a menu and tools zone, (5) a refining zone, (6) an alphanumeric sequence box 650, (7) a graphic display box 655, (8) a nucleotide base selection paddle 657, (9) a vocal verification button 680, (10) a modifications button 661 and (11) a panel of oligonucleotide statistics and measurements 659.

In this mode, the user can navigate through the order number display box 652 and the oligonucleotide ID display box. 653. The navigation buttons 654a, 654b allow access to tables with detailed information on orders or sequences. The navigation wheels 656a, 656b allow for sequential scrolling of the orders or sequences. Orders and oligonucleotide sequences in these fields are labeled with numbers and names. A scrolling menu allows the user to access the list of orders in progress and the sequences of the order in progress.

The menu and tools zone offers tools to operate the current order and/or sequence of the current order. The menu and tools zone displays three buttons: (1) Orders, (2) Sequences and (3) Tools. The Orders button allows the user to create, save, open, validate, or print an order. The Sequence button allows the user to create a new sequence, start a primer design, or import a file from a hard disk. The Tools button allows the user to search, copy selected elements, or import sequences from the clipboard.

The refining zone is a menu bar that offers ways to specify characteristics of the current order and/or the sequences of the current order. The refining zone displays three buttons: (1) Applications, (2) Options, and (3) Priorities. The Applications button allows the user to select one of several envisioned uses (e.g., PCR, sequencing, hybridization). The Options button allows the user to define the packaging, quantity, documentation, and the field of the application. The Priorities button allows the user to prioritize an order based on variables such as price, turn-around, or purity.

The alphanumeric sequence box 650 has two ends, labeled, 5' and 3', to allow for polarization of the sequence. The user can enter the desired nucleotide sequences into the box by using the authorized letters: A, C, G, T, U, I, R, Y, M, K, S, W, H, B, V, D and N. The user can control the entry of nucleotides by using the mouse.

The graphic display box 655 provides an illustrative representation of the entered oligonucleotide sequence. This box comprises a ruler to allow the user to know the position in the chain of each visible base. In addition the box displays the sequence itself which is composed of: (1) the bases 658, 662, 668, 672, 676, (2) the links between the bases 660, 664, 670, (3) the modifications of insertion, and (4) the HO and OH left and right end components. Arrows 771a, 771b, 773a, 773b allow the user to navigate towards the right and left of the displayed sequence.

Positioning the mouse cursor over any element of the sequence inside the graphic display box 655 will cause an infobubble to appear which explains the nature of the object and its state. Clicking on an element of the sequence with the mouse cursor causes a contextual floating menu to appear which offers the user all of the transformations possible on the particular element. The user is allowed to modify and delete bases, modify links, insert spacers, and insert monomers.

The nucleotide base selection paddle 657 is in the form of a cross and displays the letters A, G, C, and T on the ends. By clicking on a particular letter, the respective base will be displayed in the alphanumeric sequence box 650, and the graphic display box 655. It is also possible for the user to drag and drop a base from the paddle to the desired location inside the graphic display box 655.

When selected, the vocal verification button 680 will verbally state the sequence in progress.

The modification button 661 allows the user to modify a selected portion of a sequence in the alphanumeric sequence box 650. The modifications available to the user are dependent upon how many bases the user selects. If the user selects one base, the base may either be modified or deleted. If two or more bases are selected, the user can modify links in addition to modifying and deleting bases.

The panel of oligonucleotide statistics and measurements 659 displays a certain number of physicochemical indicators and other measurements e.g., molecular weight, size, and % GC.

Edit Order Mode

FIG. 11 shows the Edit Order Mode as a tabular presentation of all the sequences associated with an order. In this mode, the OligoPlayer displays: (1) a menu bar, (2) an order identifier 705, (3) the current sequence 706, and (4) mechanisms of selection and identification of the order and current sequences 652, 653, 654a, 654b, 656a, 656b.

The table is divided into columns that display all of the characteristics of a particular sequence, including the: (1) Oligo ID number 701, (2) Oligo name 702, (3) base number 703, (4) utilization 705, (5) priority 706 , and (6) sequence 704. A scroll bar 707 allows the user to view hidden orders.

Selecting a column name will sort the entire table in alphabetical or numerical order. There is always a blue-highlighted "current sequence" in the table. By default it is the first entry in the table, but the "current sequence" may be changed by (1) using the navigational wheel, (2) directly selecting another sequence, or (3) using the Up and Down displacement arrows. The "current sequence" is the sequence that will be graphically displayed when the user leaves the Edit Order Mode.

To change an entry in the Oligo name or base number column, the user may click on the desired cell and type in a modified entry. To change an entry in the utilization or priority column, the user may click on the desired cell, thereby transforming the cell into a scrolling menu that presents the user with available options. For example, clicking on a cell in the priority column will display the following options to the user: price, turn-around, purity, control, or alt.

The menu bar allows the user to operate on the entire order or the current order. The menu bar is comprised of three buttons: (1) Order button, (2) Sequences Button, and (3) Tool Button. The Order button allows the user to create, validate, save, open, and print an order. The Sequences button allows the user to create a new sequence, start a primer design, or import a file on the hard disk. The Tool button allows the user to search the orders or edit, delete, print, copy, or paste a sequence.

Bid Request Mode

FIG. 12 shows an illustration of the Bid Request Mode. This mode displays a tabular presentation of all the orders that are validated and thus capable of price quote or an order request. The Bid Request Mode comprises: (1) a menu bar, (2) a current order 758, (3) mechanisms of selection of the current order 654a, 656a, 652 and (4) the current order 770.

The table is divided into columns representing the following characteristics of an order: (1) order ID number 758, (2) order name 760, (3) creation date 762, (4) number of Oligos 764, (5) utilization 766, (6) priority 768, and (7) number of bases 754. There is also a special column 756

that serves as a mechanism to select various orders. The table also includes a vertical scrolling bar 772, which allows the user to view hidden orders.

Similar to the Edit Order Mode, clicking on a column name will sort the entire table in alphabetical or numerical order. There is always a blue-highlighted "current order" in the table. By default it is the first entry in the table, but the "current order" may be changed by (1) using the navigational wheel, (2) directly selecting another order, or (3) using the Up and Down displacement arrows. The "current order" is the order that will be directly displayed when the user leaves this mode.

The special column allows the user to bid on (get a price quote), or definitively order multiple orders in one transaction. All orders that are checked in the special column will be ordered or receive a price quote.

The user may change an entry in the order name, creation date, number of Oligos, or number of bases column by clicking on the desired cell and typing in a modified entry. The user may change an entry in the utilization or priority column, by clicking on the desired cell, thereby transforming the cell into a scrolling menu that presents the user with available options.

The menu bar makes it possible to start operations on: (1) the entire order list, (2) the selected order list, and (3) the current order. The menu bar comprises an Order button and a Tools button. The Order button allows the user to send the selected orders for a bid proposal or an order. The Tools button allows the user to edit, delete, or print orders.

Order Status Mode

FIG. 13 provides an illustration of the Order Status mode. This mode displays a tabular presentation of all the orders being processed. The table is divided into two sections: (1) characteristics of the order 808 and a (2) status of the order section 810.

The characteristics of the order section 808 contains the following information: (1) order ID number 812, (2) order name 813, (3) creation date 814, (4) utilization 816, (5) number of Oligos 815, (6) quote number 802, (7) order date, (8) shipment date, (9) production report, and (10) status. This section has both vertical and horizontal scrolling bars 817, 818 to visualize all the orders and all the fields of each order.

The status of the order section 810 is divided into three columns: (1) status 804, (2) waiting for 805, and (3) news 807. The status column 804 shows the current state of the order: (1) validated, (2) bid request, (3) quote available, (4) send order, (5) order acknowledge, and (6) completed. The waiting for column 805 displays the next step that will occur in the ordering process. For example if the status column shows that an order was sent out, the waiting for column will signify that the product will be sent. The news column 807 will indicate to the user whether new information regarding an order is available.

Selecting a column name sorts the entire table in alphabetical or numerical order. There is always a blue-highlighted "current order" 819 in the table. By default it is the first entry in the table, but the "current order" may be changed by (1) using the navigational wheel, (2) directly selecting another order, or (3) using the Up and Down displacement arrows. The user may access additional information about an order by opening a tabular presentation of the order, the quotation document, or the production report.

The menu bar makes it possible to start operations on: (1) the entire order list, (2) the selected order list, and (3) the current order. The menu bar comprises an Order button and a Tools button. The Order button allows the user to send the selected orders for a bid proposal, an order, or to the archive if the order is in the completed state. The Tools button allows the user to visualize the order, print the order list, and print the current order.

A. Other Embodiments

While the embodiments of the invention have been described as a system for ordering custom oligonucleotides, the system is not so limited. For example, custom antibodies, gene sequences, peptides and chemical compounds could be implemented.

Custom antibodies could be ordered by having the customer enter in the amino acid sequence of the desired antigen into the bid module 25. The bid module would convert the amino acid sequence data into a standard data format that could be read by multiple vendors. The transaction server would then forward a bid request to vendors that had signed up with the transaction server to bid on production of custom antibodies. Those vendors would then receive the XML data corresponding to the custom antigen and price producing the antibody as discussed above. In general, the vendor would take into account the cost of synthesizing the antigen, similar to the system described above, for pricing the cost of synthesizing an oligonucleotide sequence.

The cost of then manufacturing that antigen and producing either polyclonal or monoclonal antibodies from the antigen would be added into the bid price. The techniques for developing polyclonal and monoclonal antibodies from a known antigen are well known in the art, and normally involve injecting a rabbit or mouse with the antigen in order to purify an antibody that is raised against the injected antigen.

Once a bid is accepted by a customer, it is sent to the appropriate vendor who would receive the order and process the request. By using a commercially available peptide synthesizer, such as a PE Biosystems (Foster City, CA) Model 431A peptide synthesizer, the customer data can be directly transferred to the synthesizer for production. Once production of the peptide was complete, the product would be introduced into a rabbit, and polyclonal or monoclonal antibodies, depending on the customer's order, would be generated.

Similarly, the customer could enter or import nucleotide sequences corresponding to gene fragments, and request bids for production of the full-length gene. The vendors would accept XML documents having a the DNA sequence of the gene fragment, and then search internal and external databases for information on the full length gene that was requested by the customer. If the vendor found that its system included the complete DNA sequence of the gene of interest, a price would be estimated back to the customer for providing this data. If the vendor determined that it only had some, but not all, of the DNA sequence of the gene of interest, it could estimate a price for discovering the DNA sequence of the full length gene and a time estimate for that process.

The system can also be used to bid prices for single nucleotide polymorphisms (SNPs) corresponding to a known gene. For example, the customer would enter a DNA sequence in the bid module and then request bids for determining SNPs of the DNA sequence. Vendors could search their internal and external gene databases to determine if they had SNPs corresponding to the requested DNA sequence. If one or more SNPs were found by the vendor, the price for identifying these SNPs would be sent to the customer. Of course, the customer would accept bids through the transaction server from a plurality of vendors and could choose to accept data from a particular vendor based on a desired parameter, such as price, deliver, etc.

WHAT IS CLAIMED IS:

1. A system for pricing the synthesis of custom biologicals, comprising:

a first module for transmitting chemical compound parameters in a standard data format from a customer computer to a transaction server;

a second module in said transaction server comprising commands for transmitting said chemical compound parameters to a plurality of vendor systems;

a third module in said vendor system comprising commands for determining the price of said custom biological and forwarding a bid price for synthesizing said compound to said transaction server; and

a fourth module in said transaction server for compiling said bids from said plurality of vendor systems and transmitting said bids to said customer computer.

2. The system of Claim 1, wherein said standard data format is the Extensible Markup Language format.

3. The system of Claim 1, wherein said chemical compound parameters are selected from the group consisting of: amino acid parameters, oligonucleotide parameters, antibody parameters, and genomic data parameters.

4. The system of Claim 1, wherein said fourth module comprises instructions for transmitting said bids in price order to said customer.

5. The system of Claim 1, wherein said first module comprises instructions for transmitting chemical compound parameters comprising Single Nucleotide Polymorphisms of a nucleic acid sequence.

6. The system of Claim 1, wherein said first module comprises instructions for transmitting chemical compound parameters comprising allelic variants of a nucleic acid sequence.

7. A system for ordering custom oligonucleotides, comprising:

an order module configured to accept nucleotide base information and display said base information in a graphical format, wherein said graphical format comprises indicia of nucleotide bases and indicia of bonds located between said nucleotide bases.

8. The system of Claim 7, wherein said indicia of nucleotide bases comprises colored spheres representing each of the nucleotide bases.

9. The system of Claim 8, wherein said colored spheres further comprise a letter indicating the represented nucleotide base.

10. The system of Claim 7, wherein said indicia of bonds comprises a jagged lines.

11. A system for ordering custom biologicals, comprising:

a first computer module configured to accept genetic sequence data;

a second computer module configured to transmit said genetic sequence data to a transaction server, wherein said transaction server transmits said genetic sequence data to a

plurality of vendors in order to obtain pricing bids for analyzing said genetic sequence data; and

a third computer module configured to receive pricing bids from said plurality of vendors.

12. The system of Claim 11, wherein said genetic sequence data is transmitted in the Extensible Markup Language format.

13. The system of Claim 11, wherein said genetic sequence data comprises chemical compound parameters selected from the group consisting of: amino acid parameters, oligonucleotide parameters, antibody parameters, and genomic data parameters.

14. The system of Claim 11, wherein said pricing bids are transmitted in price order to said third computer module.

15. The system of Claim 11, wherein said second computer module comprises instructions for transmitting chemical compound parameters comprising Single Nucleotide Polymorphisms of a nucleic acid sequence.

16. The system of Claim 11, wherein said second computer module comprises instructions for transmitting chemical compound parameters comprising allelic variants of a nucleic acid sequence.

17. A system for ordering a portfolio of single nucleotide polymorphisms for a selected genetic sequence, comprising:

a first module for transmitting said selected genetic sequence in a standard data format from a customer computer to a transaction server;

a second module in said transaction server comprising commands for transmitting said genetic sequence to a plurality of vendor systems;

a third module in said vendor system comprising commands for matching said selected genetic sequence against a database of single nucleotide polymorphisms to determine whether any polymorphic sequences exist for the selected genetic sequence;

a fourth module in said vendor system comprising commands for determining the price of identifying said single nucleotide polymorphisms; and

a fifth module in said transaction server for compiling said bids from said plurality of vendor systems and transmitting said bids to said customer computer.

18. The system of Claim 17, wherein said standard data format is the Extensible Markup Language format.

19. The system of Claim 17, wherein said fifth module comprises instructions for transmitting said bids in price order to said customer.

20. A system for pricing the synthesis of oligonucleotides, comprising:

a first module running on a customer computer for accepting oligonucleotide sequence data;

a second module configured to determine the number of nucleotide bases and types of chemical bonds in said sequence data;

a third module configured to transmit said number of nucleotide bases and types of chemical bonds to a transaction server, but not transmitting the actual sequence of the oligonucleotide;

a fourth module configured to transmit said chemical compound parameters from said transaction server to a plurality of vendor systems;

a third module in said vendor system comprising commands for determining the price of said custom biological and forwarding a bid price for synthesizing said compound to said transaction server; and

a fourth module in said transaction server for compiling said bids from said plurality of vendor systems and transmitting said bids to said customer computer.

21. The system of Claim 20, wherein said third module is configured to transmit said nucleotide bases in the Extensible Markup Language format.

22. The system of Claim 20, wherein said types of chemical bonds are phosphorothioate or methylphosphonate bonds.

23. The system of Claim 20, wherein said fourth module comprises instructions for transmitting said bids in price order to said customer.

24. A method for pricing the synthesis of custom biological compounds, comprising:

transmitting chemical compound parameters in a standard data format from a customer computer to a transaction server;

transmitting said chemical compound parameters to a plurality of vendor systems;

determining the price of said custom biological compound;

forwarding a bid price for synthesizing said compound to said transaction server;

compiling said bids from said plurality of vendor systems; and

transmitting said bids to said customer computer.

25. The method of Claim 24, wherein said standard data format is the Extensible Markup Language format.

26. The method of Claim 24, wherein said chemical compound parameters are selected from the group consisting of: amino acid parameters, oligonucleotide parameters, antibody parameters, and genomic data parameters.

27. The method of Claim 24, wherein comprising transmitting said bids in price order to said customer.

28. The method of Claim 24, comprising transmitting chemical compound parameters comprising Single Nucleotide Polymorphisms of a nucleic acid sequence.

29. The method of Claim 24, comprising transmitting chemical compound parameters comprising allelic variants of a nucleic acid sequence.

30. A method for displaying a custom oligonucleotide, comprising:

accepting nucleotide base information into a order entry module;

displaying said base information in a graphical format, wherein said graphical format comprises indicia of nucleotide bases and indicia of bonds located between said nucleotide bases.

31. The method of Claim 30, wherein said indicia of nucleotide bases comprises colored spheres representing each of the nucleotide bases.

32. The method of Claim 31, wherein said colored spheres further comprise a letter indicating the represented nucleotide base.

33. The method of Claim 30, wherein said indicia of bonds comprises jagged lines.

34. A method for ordering custom biologicals, comprising:

accepting genetic sequence data in a first computer module;

transmitting said genetic sequence data to a transaction server;

transmitting said genetic sequence data to a plurality of vendors in order to obtain pricing bids for analyzing said genetic sequence data; and

receiving pricing bids from said plurality of vendors.

35. The method of Claim 34, wherein said genetic sequence data is transmitted to said transaction server in the Extensible Markup Language format.

36. The method of Claim 34, wherein said pricing bids are received from said plurality of vendors in price order.

37. A method for ordering a portfolio of single nucleotide polymorphisms for a selected genetic sequence, comprising:

transmitting said selected genetic sequence in a standard data format from a customer computer to a transaction server;

transmitting said chemical compound parameters to a plurality of vendor systems;

matching said selected genetic sequence against a database of single nucleotide polymorphisms to determine whether any polymorphic sequences exist for the selected genetic sequence;

determining the price of identifying said single nucleotide polymorphisms; and

compiling said bids from said plurality of vendor systems and transmitting said bids to said customer computer.

38. The method of Claim 37, wherein said standard data format is the Extensible Markup Language format.

39. The method of Claim 37, bids are compiled and transmitted in price order to said customer computer.

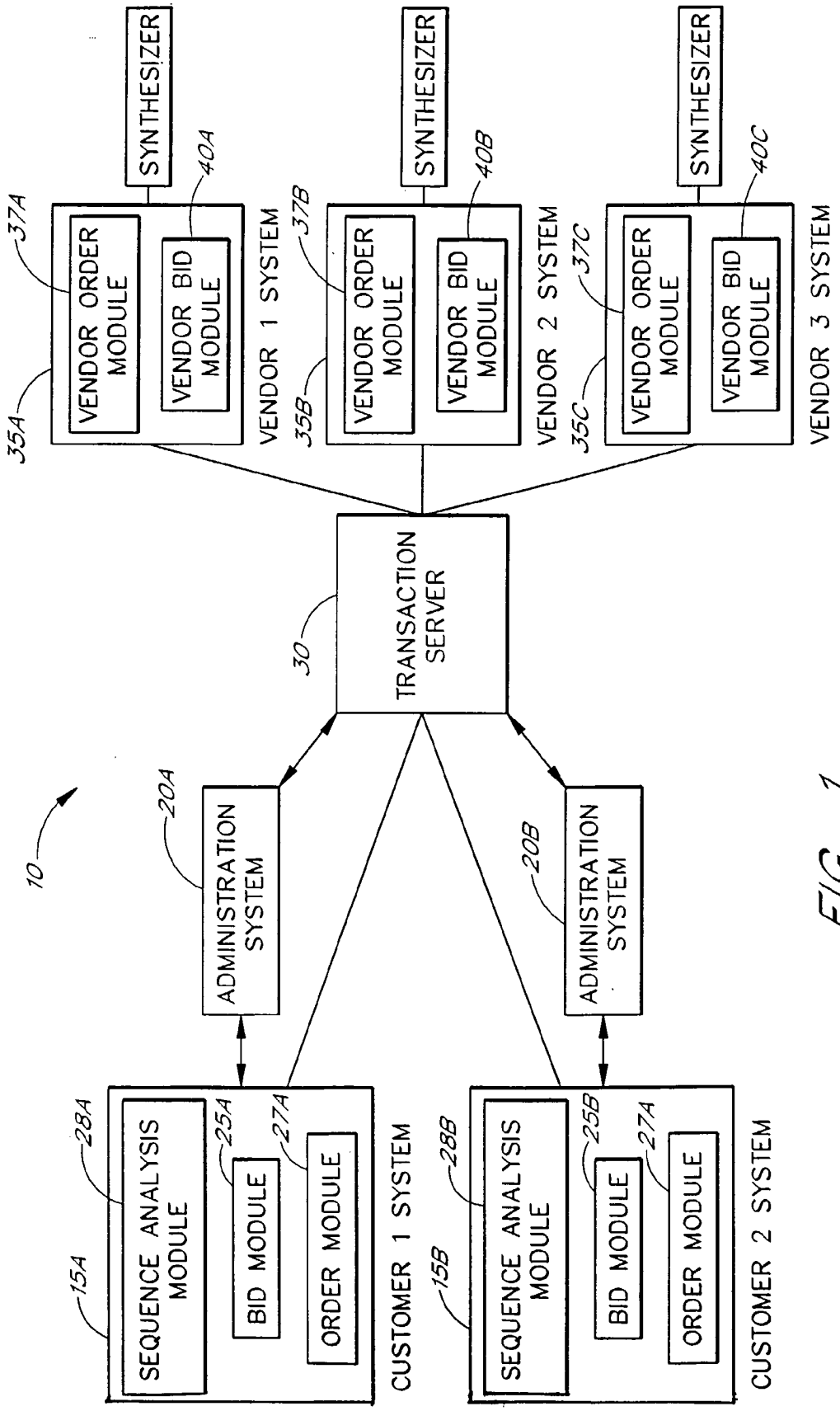
10
TRANSACTION SERVER
30
ADMINISTRATION SYSTEM
20A
ADMINISTRATION SYSTEM
20B
CUSTOMER 1 SYSTEM
CUSTOMER 2 SYSTEM
SEQUENCE ANALYSIS MODULE
BID MODULE
ORDER MODULE
15A
15B
28A
28B
25A
25B
27A
27B
VENDOR 1 SYSTEM
VENDOR 2 SYSTEM
VENDOR 3 SYSTEM
VENDOR ORDER MODULE
VENDOR BID MODULE
SYNTHESIZER
35A
35B
35C
37A
37B
37C
40A
40B
40C

FIG. 1

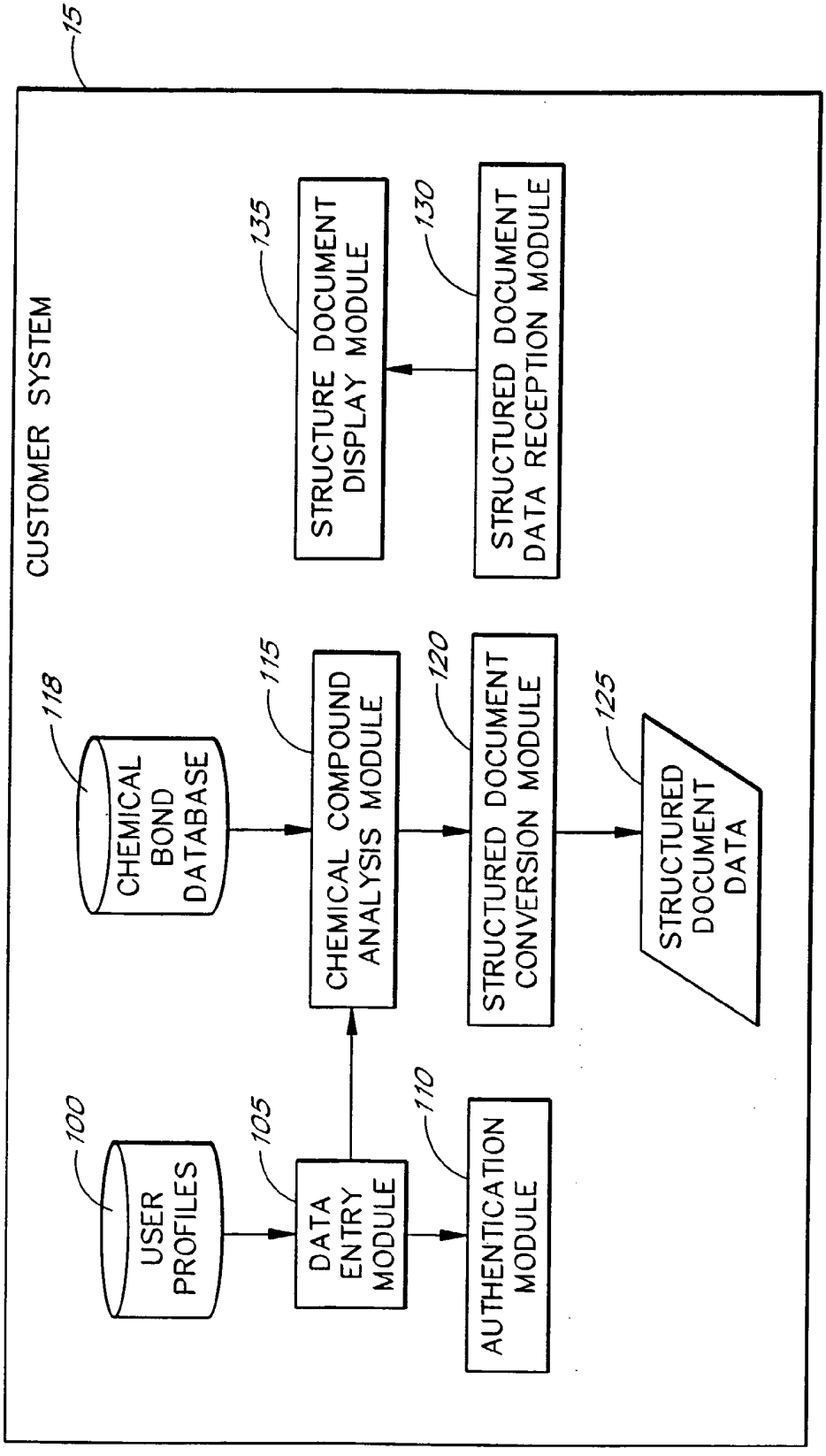
15
CUSTOMER SYSTEM
135
STRUCTURE DOCUMENT DISPLAY MODULE
130
STRUCTURED DOCUMENT DATA RECEPTION MODULE
118
CHEMICAL BOND DATABASE
115
CHEMICAL COMPOUND ANALYSIS MODULE
120
STRUCTURED DOCUMENT CONVERSION MODULE
125
STRUCTURED DOCUMENT DATA
100
USER PROFILES
105
DATA ENTRY MODULE
110
AUTHENTICATION MODULE

FIG. 2

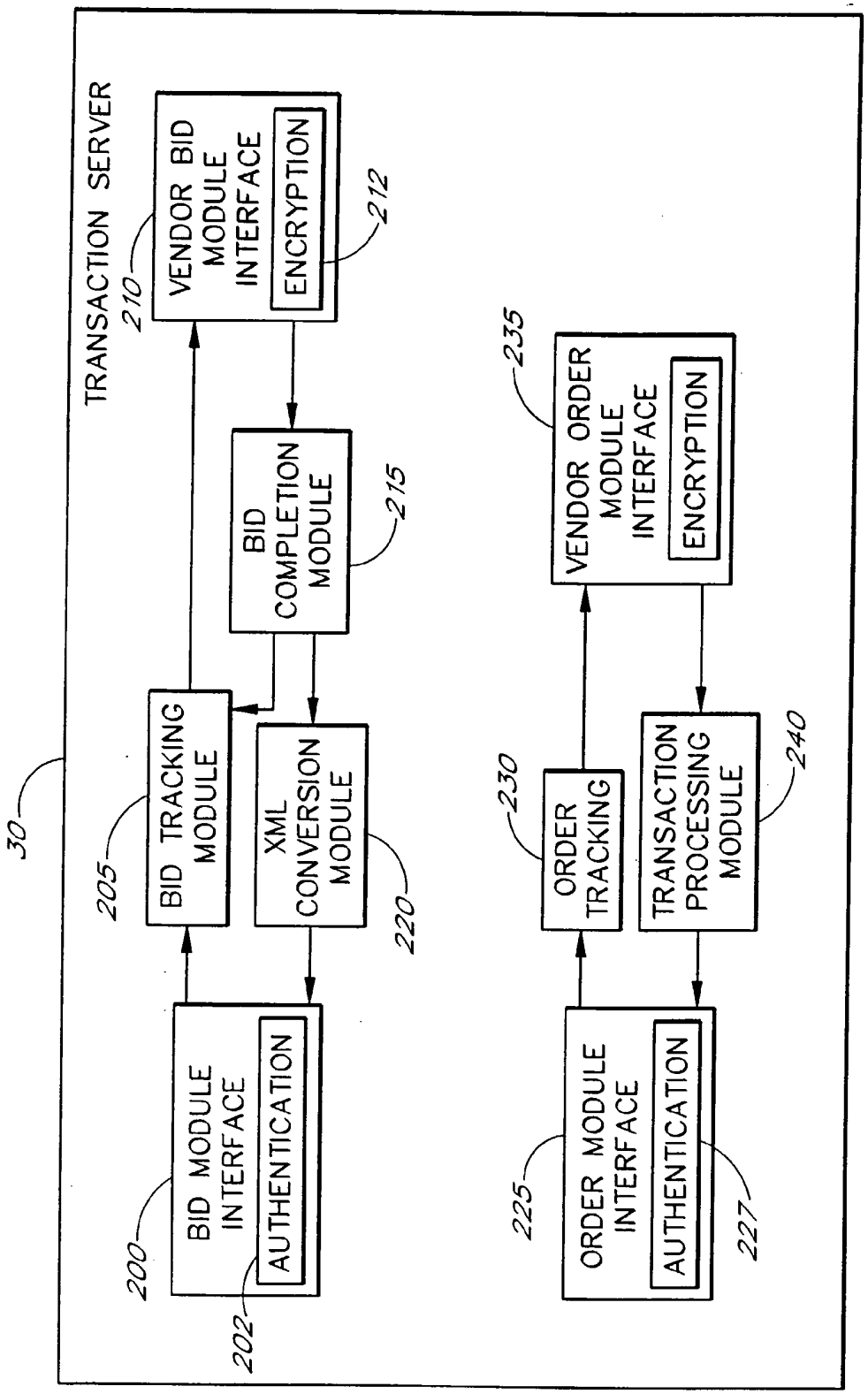
TRANSACTION SERVER
30
VENDOR BID MODULE INTERFACE
ENCRYPTION
210
212
BID COMPLETION MODULE
215
BID TRACKING MODULE
205
XML CONVERSION MODULE
220
BID MODULE INTERFACE
AUTHENTICATION
200
202
VENDOR ORDER MODULE INTERFACE
ENCRYPTION
235
ORDER TRACKING
230
TRANSACTION PROCESSING MODULE
240
ORDER MODULE INTERFACE
AUTHENTICATION
225
227

FIG. 3

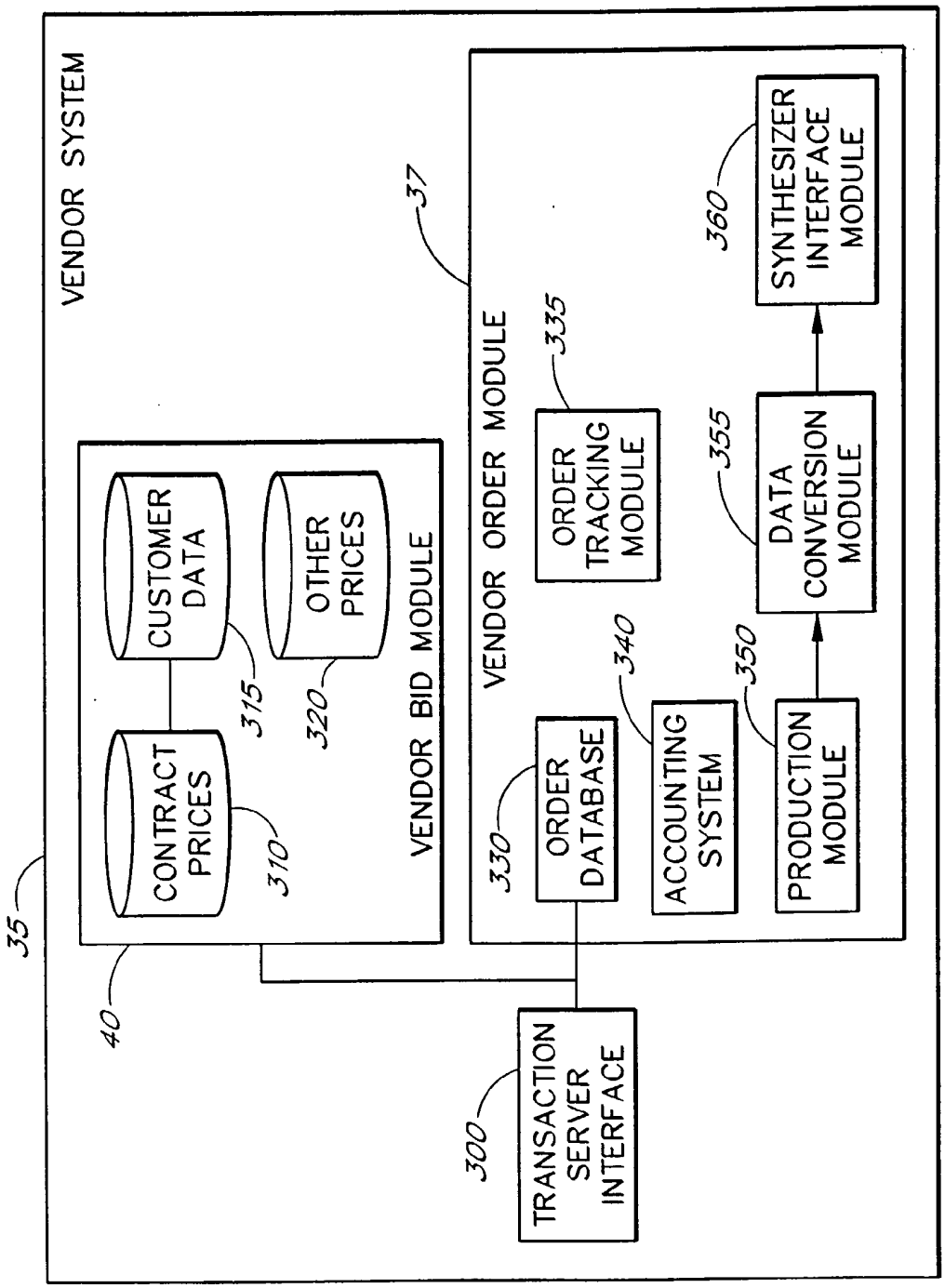
VENDOR SYSTEM
35
37
VENDOR BID MODULE
VENDOR ORDER MODULE
CUSTOMER DATA
OTHER PRICES
CONTRACT PRICES
ORDER TRACKING MODULE
ORDER DATABASE
ACCOUNTING SYSTEM
PRODUCTION MODULE
DATA CONVERSION MODULE
SYNTHESIZER INTERFACE MODULE
TRANSACTION SERVER INTERFACE
40
315
320
310
335
330
340
350
355
360
300

FIG. 4

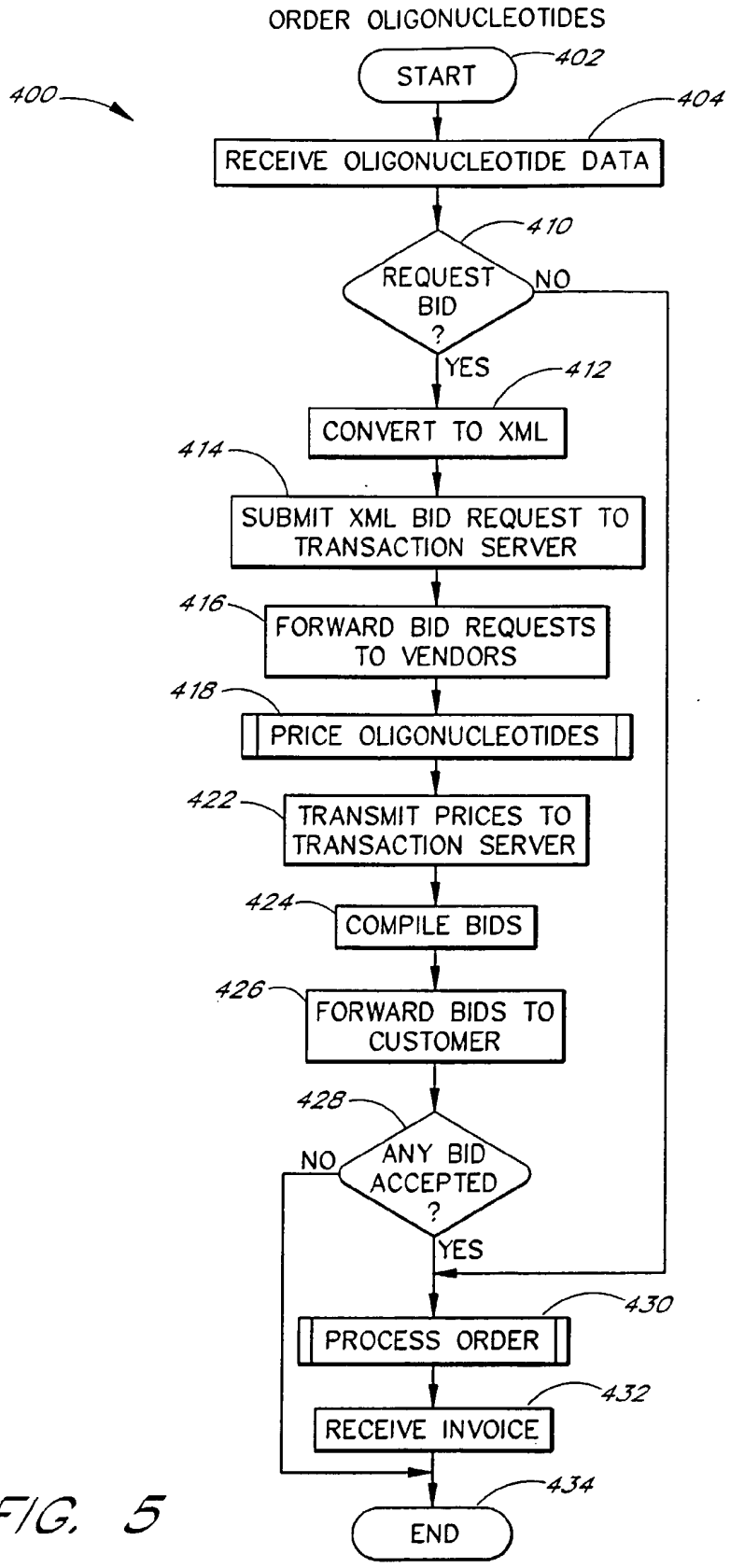
ORDER OLIGONUCLEOTIDES
400
START
402
RECEIVE OLIGONUCLEOTIDE DATA
404
REQUEST BID ?
410
NO
YES
CONVERT TO XML
412
SUBMIT XML BID REQUEST TO TRANSACTION SERVER
414
FORWARD BID REQUESTS TO VENDORS
416
PRICE OLIGONUCLEOTIDES
418
TRANSMIT PRICES TO TRANSACTION SERVER
422
COMPILE BIDS
424
FORWARD BIDS TO CUSTOMER
426
ANY BID ACCEPTED ?
428
NO
YES
PROCESS ORDER
430
RECEIVE INVOICE
432
END
434

FIG. 5

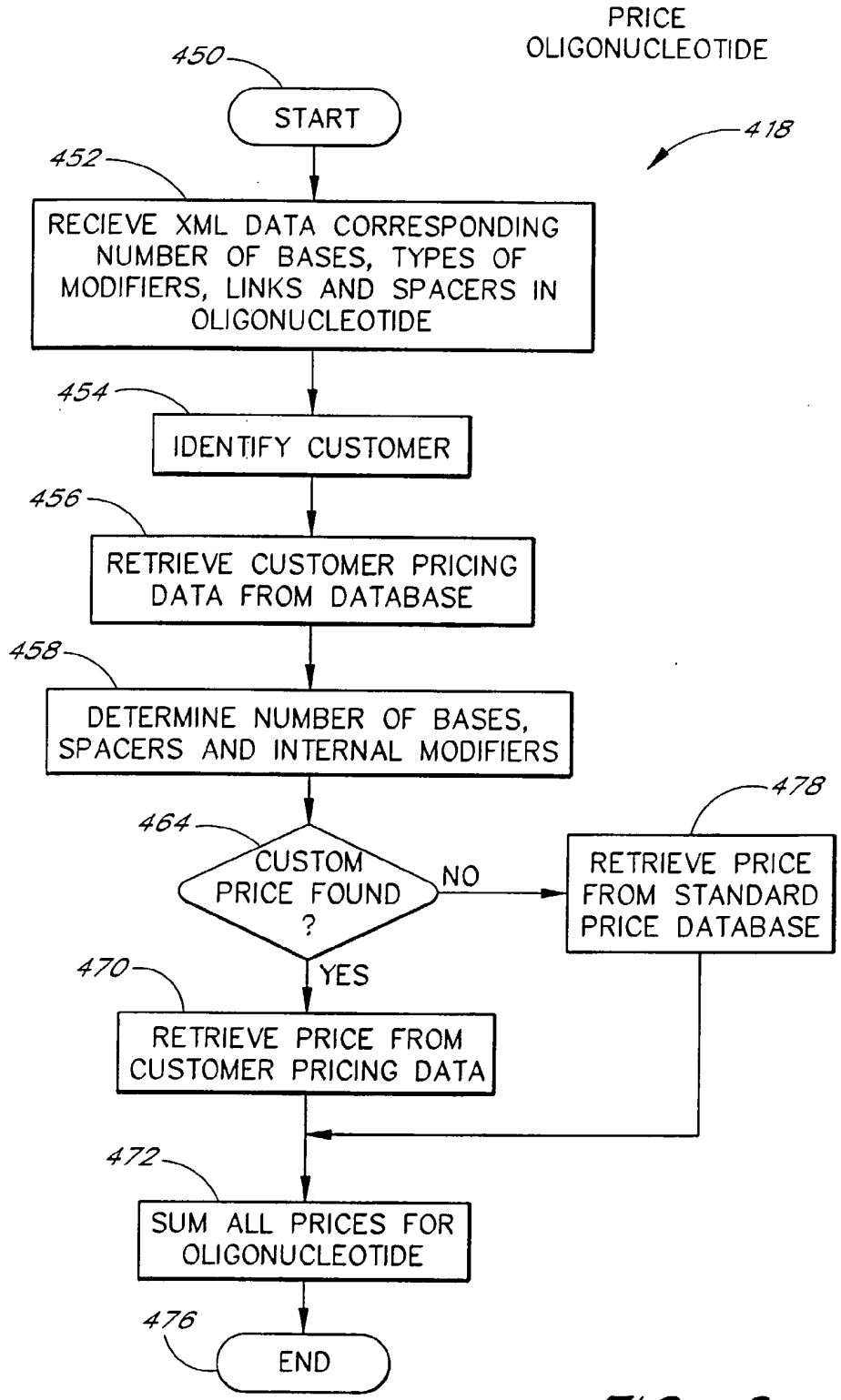
PRICE OLIGONUCLEOTIDE
418
450
START
452
RECIEVE XML DATA CORRESPONDING NUMBER OF BASES, TYPES OF MODIFIERS, LINKS AND SPACERS IN OLIGONUCLEOTIDE
454
IDENTIFY CUSTOMER
456
RETRIEVE CUSTOMER PRICING DATA FROM DATABASE
458
DETERMINE NUMBER OF BASES, SPACERS AND INTERNAL MODIFIERS
464
CUSTOM PRICE FOUND ?
NO
478
RETRIEVE PRICE FROM STANDARD PRICE DATABASE
YES
470
RETRIEVE PRICE FROM CUSTOMER PRICING DATA
472
SUM ALL PRICES FOR OLIGONUCLEOTIDE
476
END

FIG. 6

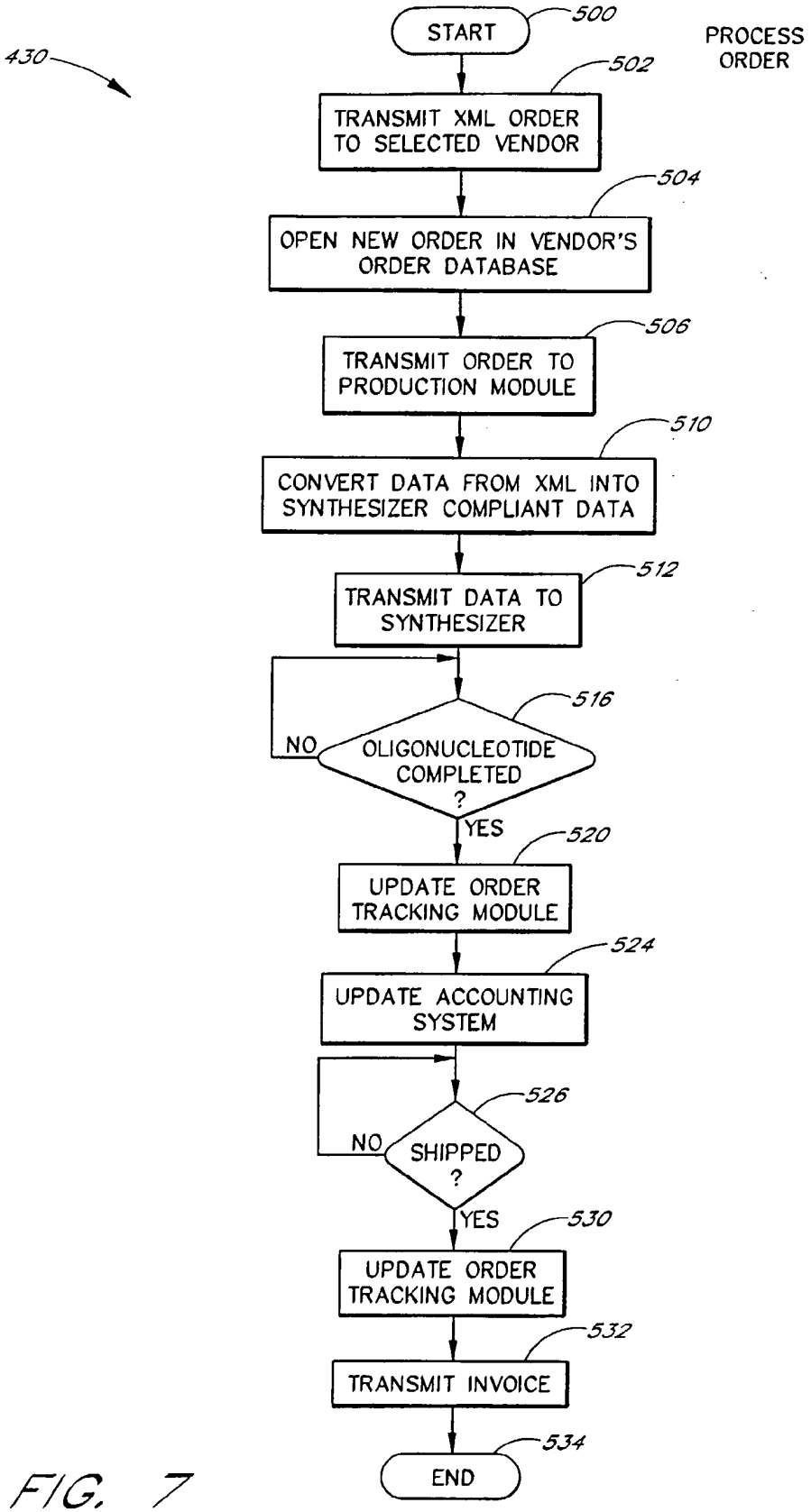
430
PROCESS ORDER
START
500
TRANSMIT XML ORDER TO SELECTED VENDOR
502
OPEN NEW ORDER IN VENDOR'S ORDER DATABASE
504
TRANSMIT ORDER TO PRODUCTION MODULE
506
CONVERT DATA FROM XML INTO SYNTHESIZER COMPLIANT DATA
510
TRANSMIT DATA TO SYNTHESIZER
512
OLIGONUCLEOTIDE COMPLETED ?
516
NO
YES
UPDATE ORDER TRACKING MODULE
520
UPDATE ACCOUNTING SYSTEM
524
SHIPPED ?
526
NO
YES
UPDATE ORDER TRACKING MODULE
530
TRANSMIT INVOICE
532
END
534

FIG. 7

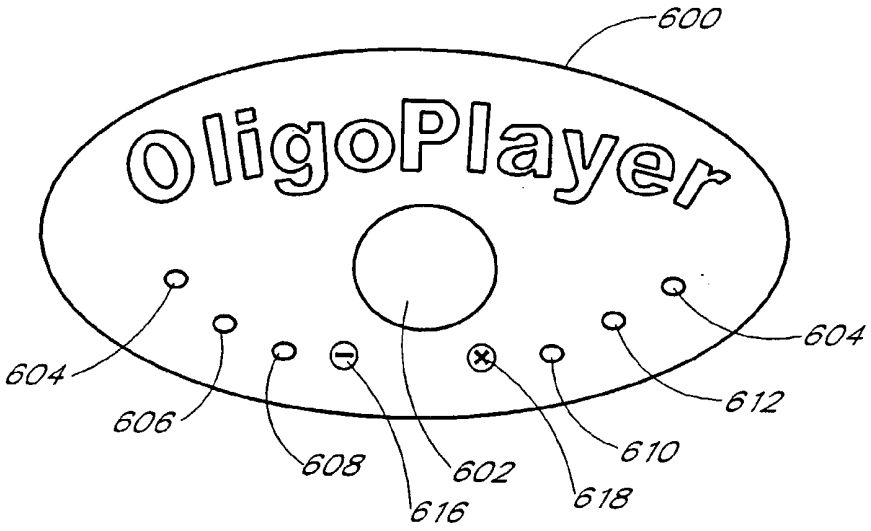

FIG. 8

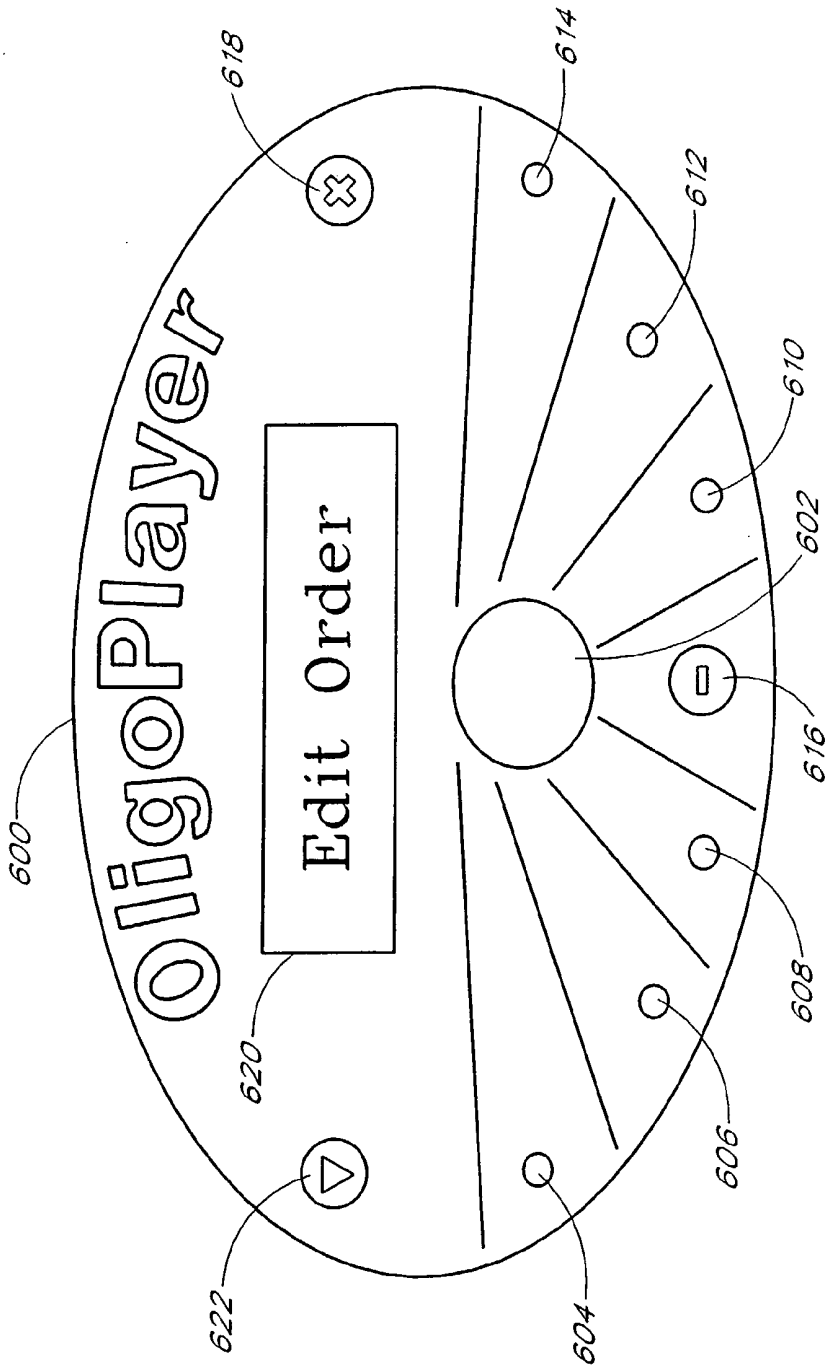
OligoPlayer
Edit Order
600
602
604
606
608
610
612
614
616
618
620
622

FIG. 9

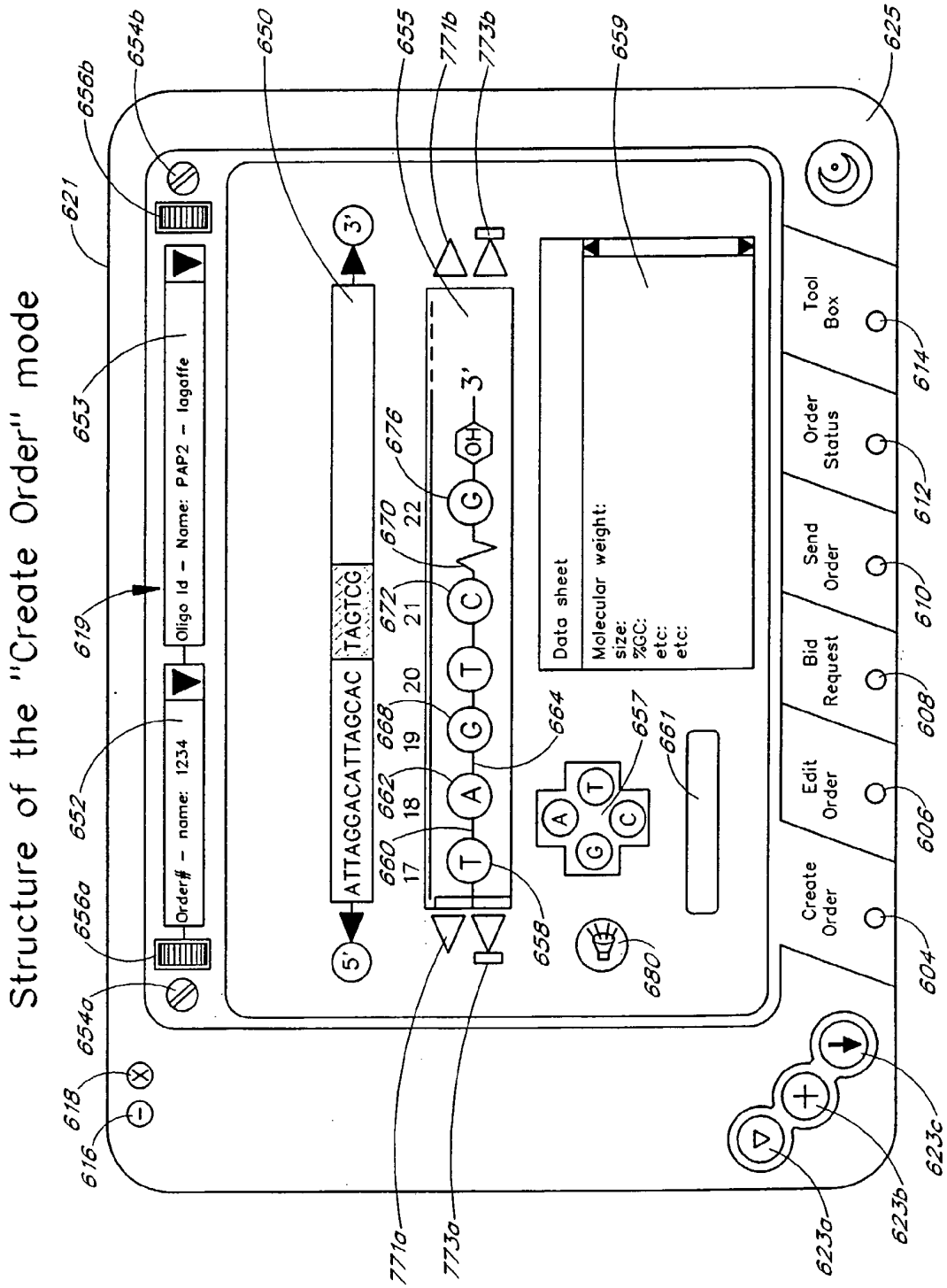
Structure of the "Create Order" mode
Order# - name: 1234
Oligo Id - Name: PAP2 - lagaffe
ATTAGGACATTAGCAC
TAGTCG
5'
3'
3'
OH
Data sheet
Molecular weight:
size:
%GC:
etc:
etc:
Create Order
Edit Order
Bid Request
Send Order
Order Status
Tool Box
604
606
608
610
612
614
616
618
619
621
623a
623b
623c
625
650
652
653
654a
654b
655
656a
656b
657
658
659
660
661
662
664
668
670
672
676
680
771a
773a
771b
773b

FIG. 10

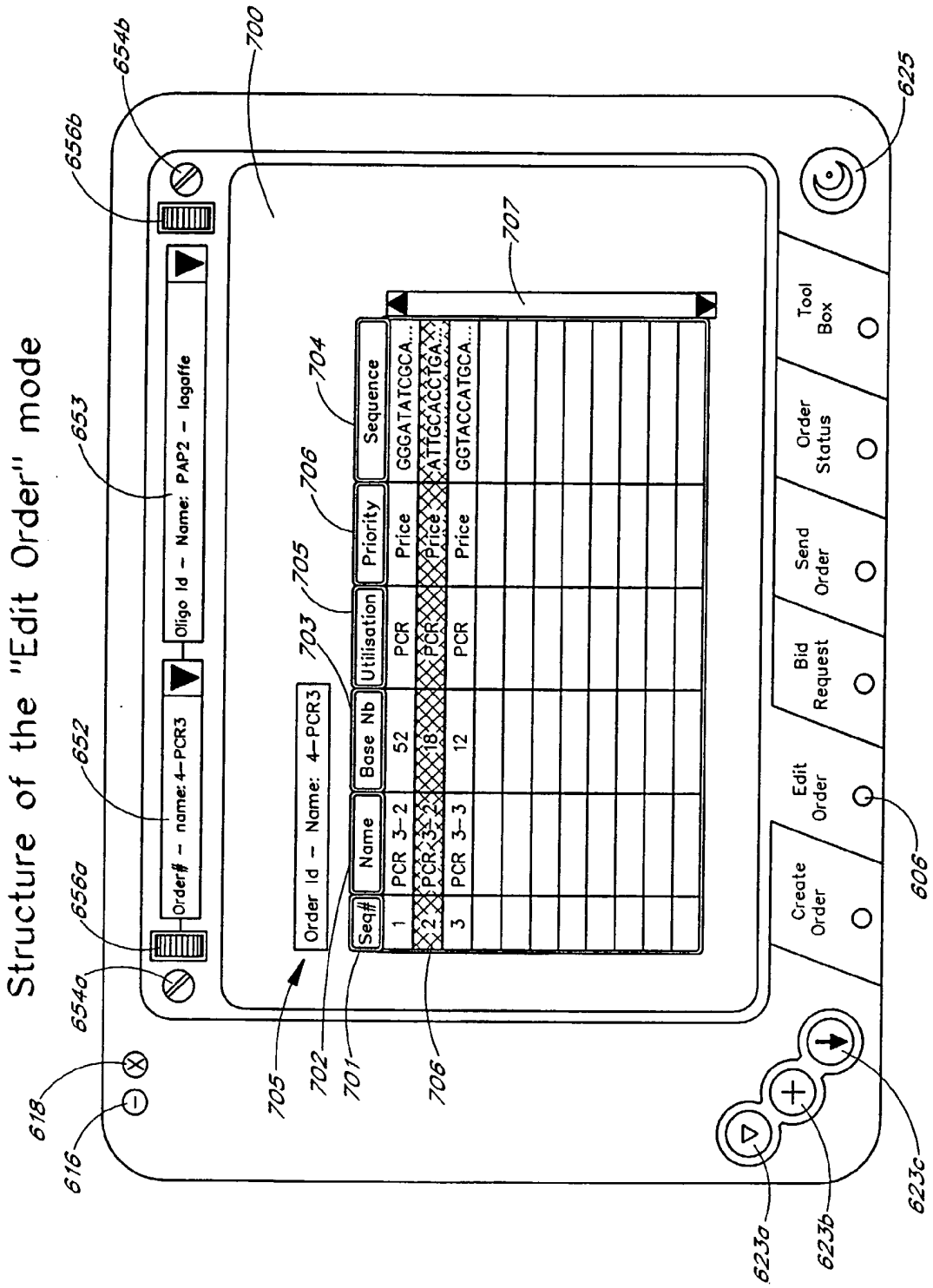
Structure of the "Edit Order" mode
700
6546
6566
653
652
6560
6540
618
616
625
606
623c
623b
623a
Order# - name: 4-PCR3
Oligo Id - Name: PAP2 - lagaffe
Order Id - Name: 4-PCR3
Seq#
Name
Base Nb
Utilisation
Priority
Sequence
1
PCR 3-2
52
PCR
Price
GGGATATCGCA...
2
PCR 3-2
18
PCR
Price
ATTCCACCTGA...
3
PCR 3-3
12
PCR
Price
GGTACCATGCA...
701
702
703
704
705
706
707
Create Order
Edit Order
Bid Request
Send Order
Order Status
Tool Box

FIG. 11

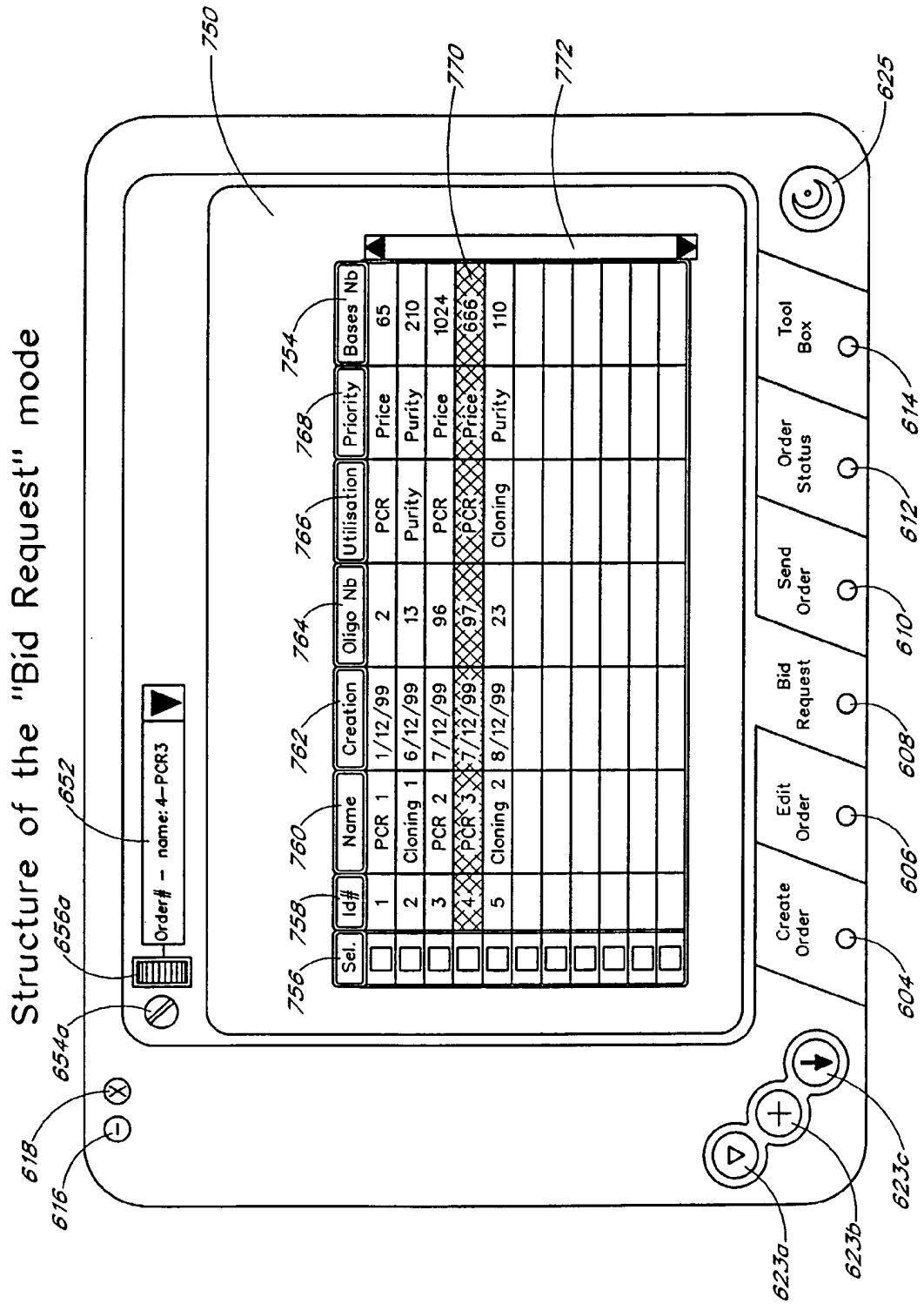
Structure of the "Bid Request" mode
750
770
772
625
652
Order# - name: 4-PCR3
656a
654a
618
616
Sel.
Id#
Name
Creation
Oligo Nb
Utilisation
Priority
Bases Nb
1 PCR 1 1/12/99 2 PCR Price 65
2 Cloning 1 6/12/99 13 Purity Purity 210
3 PCR 2 7/12/99 96 PCR Price 1024
4 PCR 3 7/12/99 97 PCR Price 666
5 Cloning 2 8/12/99 23 Cloning Purity 110
Create Order
Edit Order
Bid Request
Send Order
Order Status
Tool Box
604
606
608
610
612
614
623a
623b
623c

FIG. 12

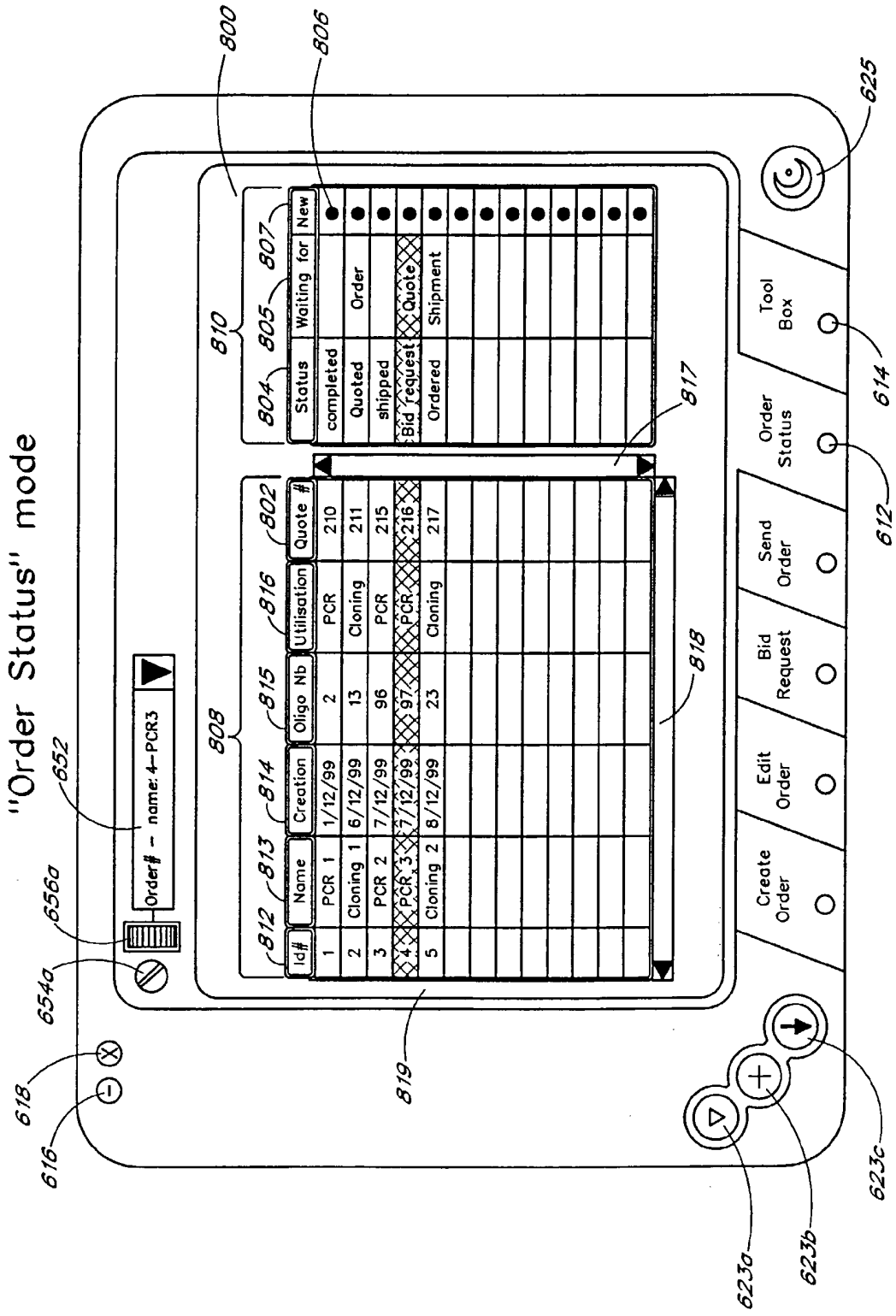
"Order Status" mode
800
806
625
652
656a
654a
618
616
810
804
805
807
Status
Waiting for
New
completed
Quoted
Order
shipped
Bid request
Quote
Ordered
Shipment
808
812
813
814
815
816
802
Id#
Name
Creation
Oligo Nb
Utilisation
Quote #
1 PCR 1 1/12/99 2 PCR 210
2 Cloning 1 6/12/99 13 Cloning 211
3 PCR 2 7/12/99 96 PCR 215
4 PCR 3 7/12/99 97 PCR 216
5 Cloning 2 8/12/99 23 Cloning 217
817
818
819
Order# - name: 4-PCR3
Create Order
Edit Order
Bid Request
Send Order
Order Status
Tool Box
612
614
623a
623b
623c

FIG. 13

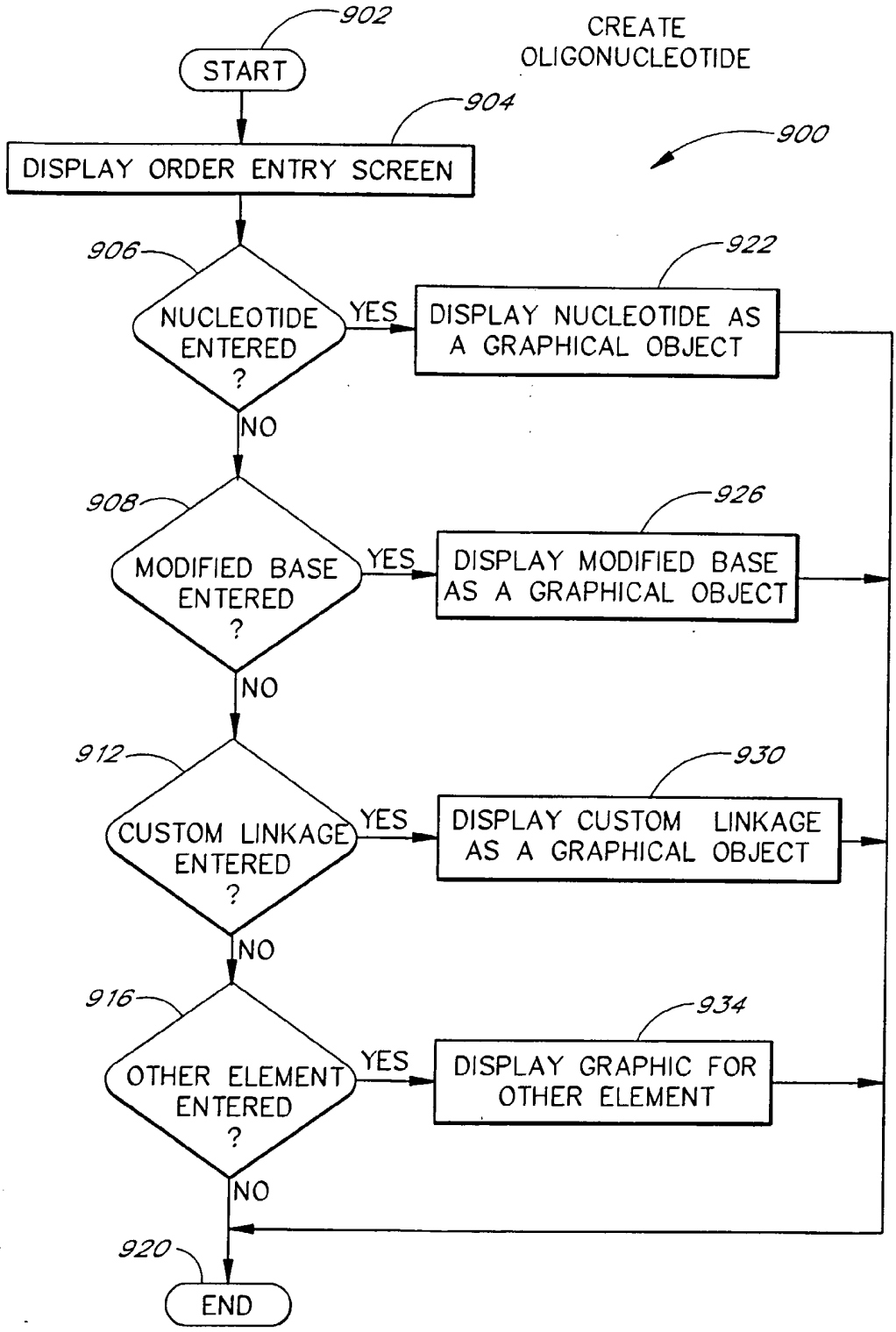
902
START
CREATE OLIGONUCLEOTIDE
904
DISPLAY ORDER ENTRY SCREEN
900
906
NUCLEOTIDE ENTERED ?
YES
922
DISPLAY NUCLEOTIDE AS A GRAPHICAL OBJECT
NO
908
MODIFIED BASE ENTERED ?
YES
926
DISPLAY MODIFIED BASE AS A GRAPHICAL OBJECT
NO
912
CUSTOM LINKAGE ENTERED ?
YES
930
DISPLAY CUSTOM LINKAGE AS A GRAPHICAL OBJECT
NO
916
OTHER ELEMENT ENTERED ?
YES
934
DISPLAY GRAPHIC FOR OTHER ELEMENT
NO
920
END

FIG. 14

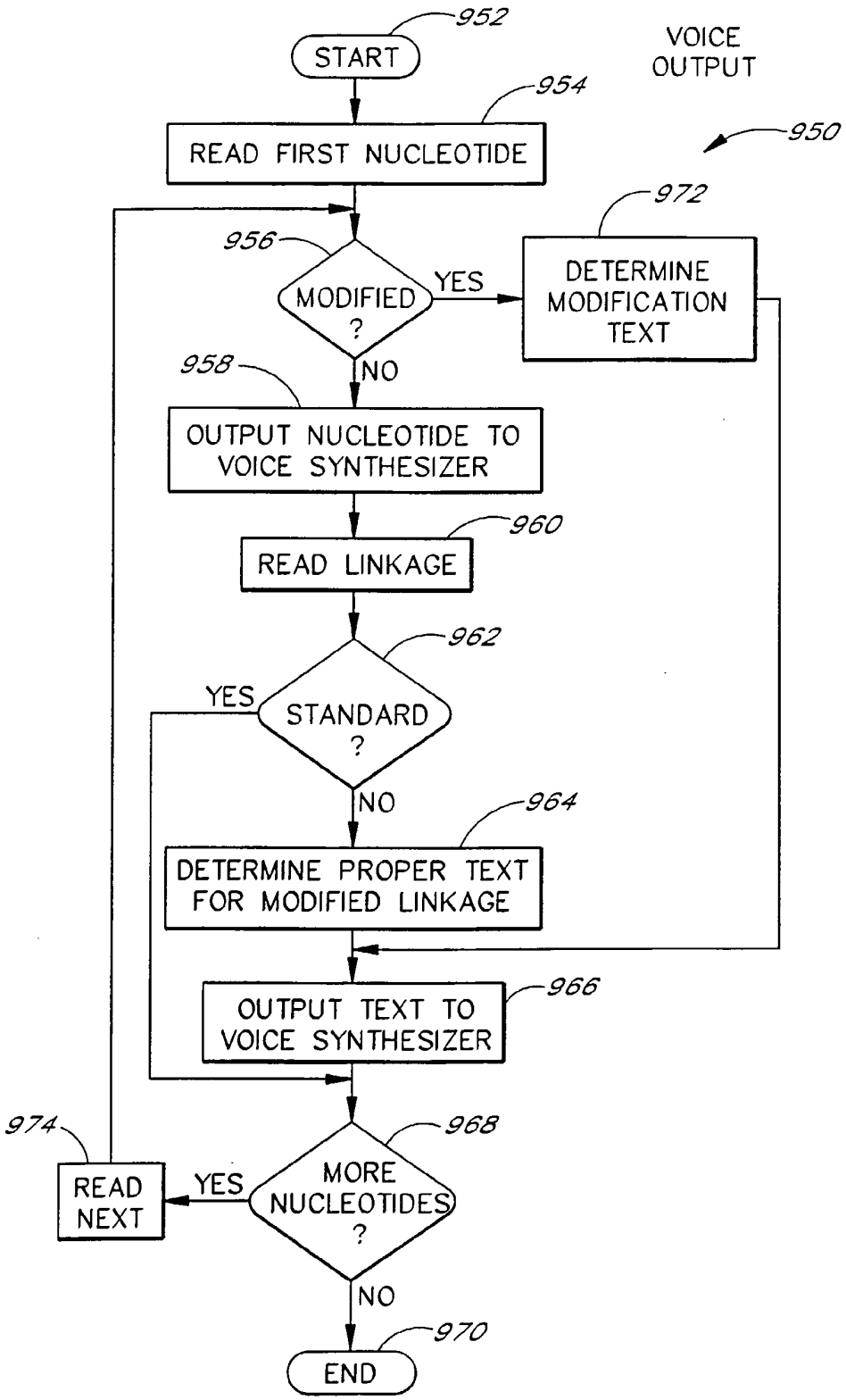
952
START
VOICE OUTPUT
954
READ FIRST NUCLEOTIDE
950
972
956
MODIFIED ?
YES
DETERMINE MODIFICATION TEXT
958
NO
OUTPUT NUCLEOTIDE TO VOICE SYNTHESIZER
960
READ LINKAGE
962
YES
STANDARD ?
NO
964
DETERMINE PROPER TEXT FOR MODIFIED LINKAGE
966
OUTPUT TEXT TO VOICE SYNTHESIZER
974
968
READ NEXT
YES
MORE NUCLEOTIDES ?
NO
970
END

FIG. 15

PATENT COOPERATION TREATY

PCT

DECLARATION OF NON-ESTABLISHMENT OF INTERNATIONAL SEARCH REPORT

(PCT Article 17(2)(a), Rules 13ter.1(c) and Rule 39)

Applicant's or agent's file reference	IMPORTANT DECLARATION	Date of mailing *(day/month/year)*
79.W01		15/06/2001
International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/IB 01/00468	13/03/2001	15/03/2000
International Patent Classification (IPC) or both national classification and IPC	G06F17/60 G06F17/50	
Applicant		
GENSET et al.		

This International Searching Authority hereby declares, according to Article 17(2)(a), that **no international search report will be established** on the international application for the reasons indicated below

1. [X] The subject matter of the international application relates to:
   - a. [ ] scientific theories.
   - b. [ ] mathematical theories
   - c. [ ] plant varieties.
   - d. [ ] animal varieties.
   - e. [ ] essentially biological processes for the production of plants and animals, other than microbiological processes and the products of such processes.
   - f. [X] schemes, rules or methods of doing business.
   - g. [ ] schemes, rules or methods of performing purely mental acts.
   - h. [ ] schemes, rules or methods of playing games.
   - i. [ ] methods for treatment of the human body by surgery or therapy.
   - j. [ ] methods for treatment of the animal body by surgery or therapy.
   - k. [ ] diagnostic methods practised on the human or animal body.
   - l. [ ] mere presentations of information.
   - m. [ ] computer programs for which this International Searching Authority is not equipped to search prior art.

2. [ ] The failure of the following parts of the international application to comply with prescribed requirements prevents a meaningful search from being carried out:
   [ ] the description [ ] the claims [ ] the drawings

3. [ ] The failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions prevents a meaningful search from being carried out:
   [ ] the written form has not been furnished or does not comply with the standard.
   [ ] the computer readable form has not been furnished or does not comply with the standard.

4. Further comments:

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mar'a Rodr'guez Nõvoa

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 203

The subject-matter claimed in claims 24-39 falls under the provisions of Article 17(2)(a)(i) and Rule 39.1(iii), PCT, such subject-matter relating to a method of doing business.

Claims 1-23 relate to a conventional system for performing the business method of claims 24-39. Although these claims do not literally belong to the method category, they essentially claim protection for the same commercial effect as the method claims. The International Searching Authority considers that searching this subject-matter would serve no useful purpose. It is not at present apparent how the subject-matter of the present claims may be considered defensible in any subsequent examination phase in front of the EPO as International Preliminary Examining Authority with regard to the provisions of Article 33(1) PCT (novelty, inventive step); see also Guidelines B-VII, 1-6).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.